DEVELOPMENT OF NEWER METHODOLOGIES AND THEIR APPLICATIONS IN THE SYNTHESIS OF USEFUL CHIRAL INTERMEDIATES AND STUDIES TOWARDS THE SYNTHESIS OF ZOAPATANOL VIA RADICAL CYCLISATION APPROACH

A Thesis Submitted
in Partial Fulfilment of the Requirements
for the Degree of
DOCTOR OF PHILOSOPHY

by

INDRANI BHATTACHARYA

to the

DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY KANPUR

JUNE, 1994

Dedicated
To
The World of Science

CONTENTS

STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology, Kanpur, India under the supervision of Prof. Y.D. Vankar.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

Indrani Bhattacharya

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Kanpur

June, 1994.

DEPARTMENT OF CHEMISTRY
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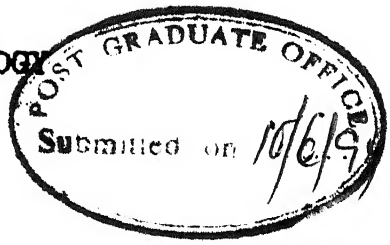
KANPUR, INDIA



CERTIFICATE - I

This is to certify that Ms. Indrani Bhattacharya has satisfactorily completed all the courses required for the Ph.D. degree programme. These courses include:

CHM 602 Advanced Organic Chemistry

CHM 605 Principles of Organic Chemistry

CHM 624 Modern Physical Methods in Chemistry

CHM 625 Principles of Physical Chemistry

CHM 645 Principles of Inorganic Chemistry

CHM 681 Basic Biological Chemistry

CHM 800 General Seminar

CHM 801 Graduate Seminar

CHM 900 PG Research

Ms. Indrani Bhattacharya successfully completed her Ph.D. qualifying examination in March 1990 after she successfully completed the written and oral qualifying examinations.

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CERTIFICATE - II

It is certified that the work contained in the thesis entitled "DEVELOPMENT OF NEWER METHODOLOGIES AND THEIR APPLICATIONS IN THE SYNTHESIS OF USEFUL CHIRAL INTERMEDIATES AND STUDIES TOWARDS THE SYNTHESIS OF ZOAPATANOL VIA RADICAL CYCLISATION APPROACH" has been carried out by Ms. Indrani Bhattacharya under my supervision and the same has not been submitted elsewhere for a degree.

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ABSTRACT

The thesis is divided into three chapters as outlined below:

CHAPTER I: SYNTHESIS OF ACHIRAL AND CHIRAL VINYL EPOXIDES FROM GLYCIDIC ESTERS VIA α- HYDROXY - β, γ -UNSATURATED ESTERS

Glycidic esters, upon isomerisation with BF_3. Et_2O, yield α- hydroxy - β, γ - unsaturated esters. These are then reduced with $LiAlH_4$ to vicinal diols which are converted to vinyl epoxides in two steps. Studies related to the synthesis of chiral vinyl epoxides are also made via two different approaches. In an effort to synthesise optically active vinyl epoxide via asymmetric induction approach glycidic esters, in which the ester moiety is derived from (-) menthol, are used. Sequence of reactions remains the same as followed in the case of achiral vinyl epoxides. In another approach chiral α-hydroxy- β, γ - unsaturated esters are procured through enzymatic resolution which are crucial intermediates for the synthesis of chiral vinyl epoxides. One such transformation has been carried out from cyclohexane system.

CHAPTER II: SYNTHESIS AND REACTIONS OF SOME USEFUL SULFUR CONTAINING SYNTHONS.

Two sets of allylic acetates derived from cyclopentane and cyclohexane systems containing vinyl sulfide and allyl sulfide units have been subjected to PLAP hydrolysis to obtain eight optically active compounds. Vinyl sulfide containing compounds have been found to give better optical yields.

An interesting synthon containing a quaternary carbon atom has been found to form as a side product. In addition to this 2-phenylthiocyclopent-2-enone, one of the precursors for the above study, has been converted into some useful intermediates which could be converted into prostaglandins and other cyclopentane natural products.

CHAPTER III: RADICAL CYCLISATION APPROACH TOWARDS THE SYNTHESIS OF ZOAPATANOL.

This chapter deals with a model study towards the synthesis of zoapatanol (1). The oxepane ring was constructed by radical induced C-C bond formation. Benzaldehyde was converted to compound **40** which was further O-allylated to obtain **41**. This was an important intermediate which was used to reach the goal. Two methodologies were adopted to get oxepane system. In the first approach oxymercurials **42A** and **42B**, were converted to the oxepane systems **43** and **45**, albeit in very low yields (~ 8%). Two other products were also obtained along with the desired one in each case. These are the reduced products **44** and **46**, and the eliminated product **41**. However, in both the cases the major product was the eliminated product **41**. Ligand exchange reaction was also attempted with **42A** to obtain **42C** which was reacted with $NaBH_4$. It was expected to find a change in product distribution, however, no significant change was observed.

In the second approach halohydrins (**47**, **48**) were synthesised from O-allylated product **41**. The methodology applied here to effect the cyclisation was the TBTH/AIBN induced radical

cyclisation of these halohydins. The crude product from both the reactions were acetylated and the two acetoxy compounds (**43** and **44**) were isolated. The major product among the two in both the cases was **44**. Further, the halohydrins were converted to haloacetates (**49** and **50**) and their radical cyclisations with TBTH/AIBN were also studied. In this case the yield of cyclised product was slightly better than the previous cases.

ACKNOWLEDGEMENTS

I would like to take this opportunity to thank my supervisor Professor Y.D. Vankar for his valuable guidance in all stages of my research work. Words will not be adequate to quantify his immense patience, tolerance and understanding. With untiring stimulating discussions and active involvement he has helped me in understanding the subject. I am highly indebted to him for his exemplary supervision and guidance. It has been a pleasure working with him and I consider myself extremely fortunate for being his student.

I would also like to express my gratitude towards Dr. P.S. Vankar (Padmadi) for her expert guidance and continued encouragement during the course of my thesis work. I will never forget her warmth friendliness and the help that I got from her all through my research work was like a boon. I'll remain grateful to her forever.

My special thanks and indebtedness are due to Dr. K.P. Madhusudanan of C.D.R.I. Lucknow for the mass spectral analyses of numerous compounds reported in this thesis.

I will never forget the cooperation and unreserved help which I got from my friends Chowdhuri da, Kavitadi, Venkat, Sangeeta, Kumar, Nitin, Anindya, Kamaljeet, Bharat, Kamal, Damu, Arpita, Sushil, Aparna, Debnath, Vandana, Anjalidi, and Bishakha. I extend my gratitude to them.

I am thankful to Mr. Nayab Ahmed for his valuable help in recording the spectra. I duly acknowledge Mr. V.N. Katiyar for typing the manuscript and Mr. Bajpai for the figure shown in the thesis with lots of patience.

The financial supports from the authorities of I.I.T. Kanpur are gratefully acknowledged.

This thesis has proved to be a turning point in my life, during the course of which I have learnt something more than my subject. I hope it has made me a better person with new perspectives in life.

CHAPTER I

SYNTHESIS OF ACHIRAL AND CHIRAL VINYL EPOXIDES FROM GLYCIDIC ESTERS VIA α -HYDROXY- β, γ - UNSATURATED ESTERS

INTRODUCTION

I.1. Reactions of Vinyl Epoxides

Vinyl epoxides are useful intermediates in organic synthesis. They contain four adjacent functionalised carbons which are potentially capable of undergoing reactions with different reagents. The presence of two functional groups in such close proximity confers interesting and useful chemistry on these compounds.

The most extensively studied reaction of these compounds is nucleophilic addition[1-5]. In principle, reaction of the monoepoxide of a 1,3 diene can lead to different products. Addition of a nucleophile to the least hindered carbon of **1** affords the 1,2 adduct **2** (path a) (Fig. 1).

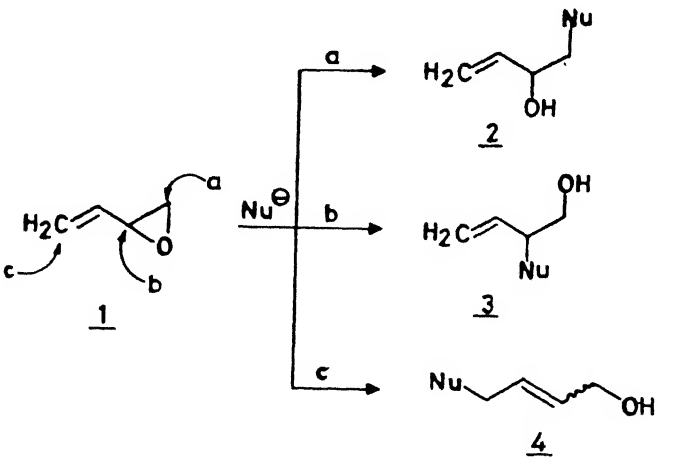
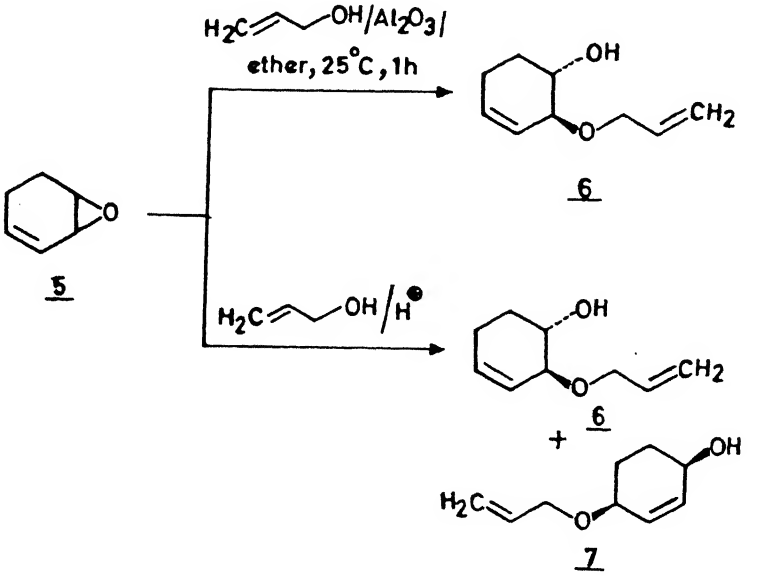


Figure 1

Alternatively, nucleophilic attack at the end of epoxide which is adjacent to the carbon carbon double bond, that is the epoxide carbon best able to stabilize an intermediate positive charge by

conjugation, affords **3** (path b). Finally, addition of the nucleophile to the double bond in an S_N2 type reaction affords the 1,4 addition product **4** (path c) [Fig. 1]. Early work on this reaction demonstrates that there is often a balance between the product **2** and the product **3**. Reagents with more steric bulk tend to attack by path 'a' but under acidic reaction conditions attack by path 'b' usually becomes the favoured reaction and many nucleophiles give mixtures of **2, 3, and 4**[6]. Some examples of these reactions are described in the following pages.



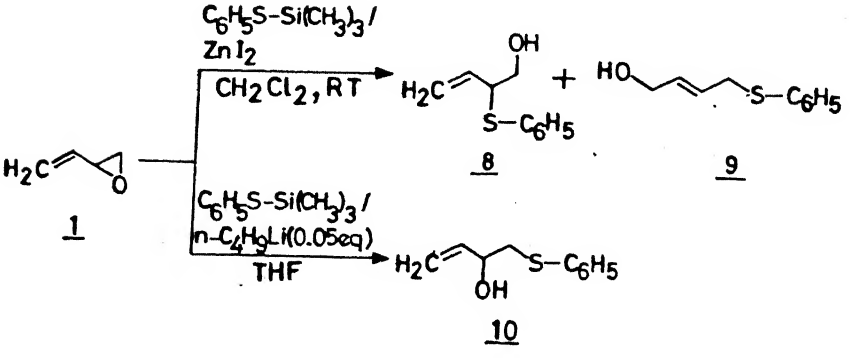


Figure 2

Treatment of 1,3-cyclohexadiene monoepoxide **5** (Fig. 2) with allyl alcohol in the presence of alumina affords only **6** the 1,2 adduct. This contrasts with the opening of **5** (Fig. 2) under homogeneous conditions in which both 1,2 and 1,4 adducts are observed.

The reaction of 1,3 diene monoepoxides with various sulfur nucleophiles has recently been examined[7-10]. Butadiene monooxide in the presence of zinc iodide reacts with trimethylsilyl phenyl sulfide to give the 1,2 adduct **8**[8]. A complete reversal in regiochemistry is observed with this reagent in the presence of n-butyllithium and compound **10** (Fig. 2) is formed.

The reaction of isoprene oxide **11** (Fig. 3) with either thiophenol and triethylamine or with diethylaluminum benzenethiolate is reported to give 1,4 adduct to afford **12** (E or Z) but

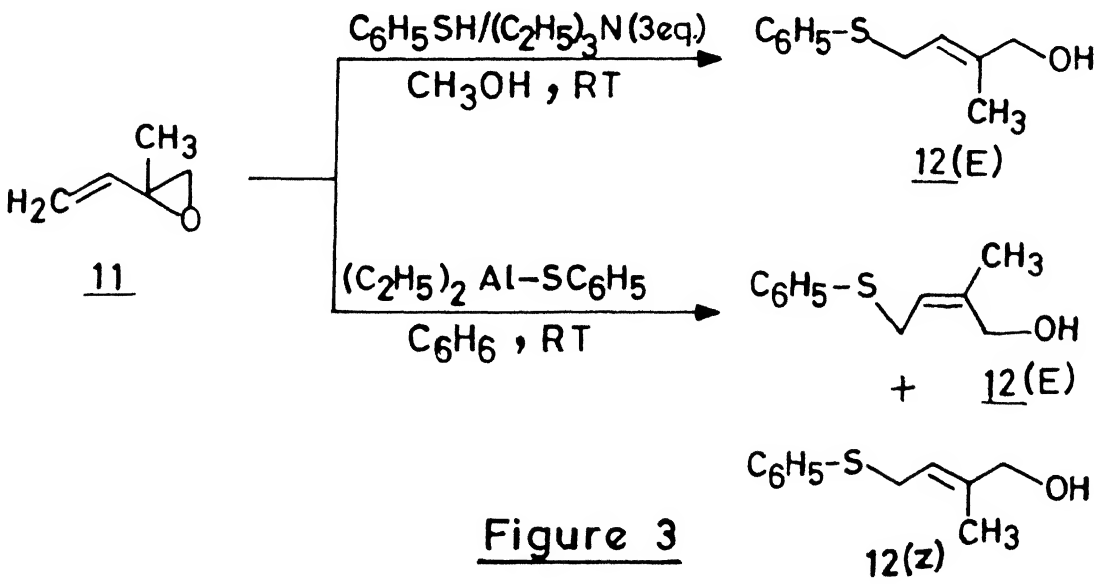


Figure 3

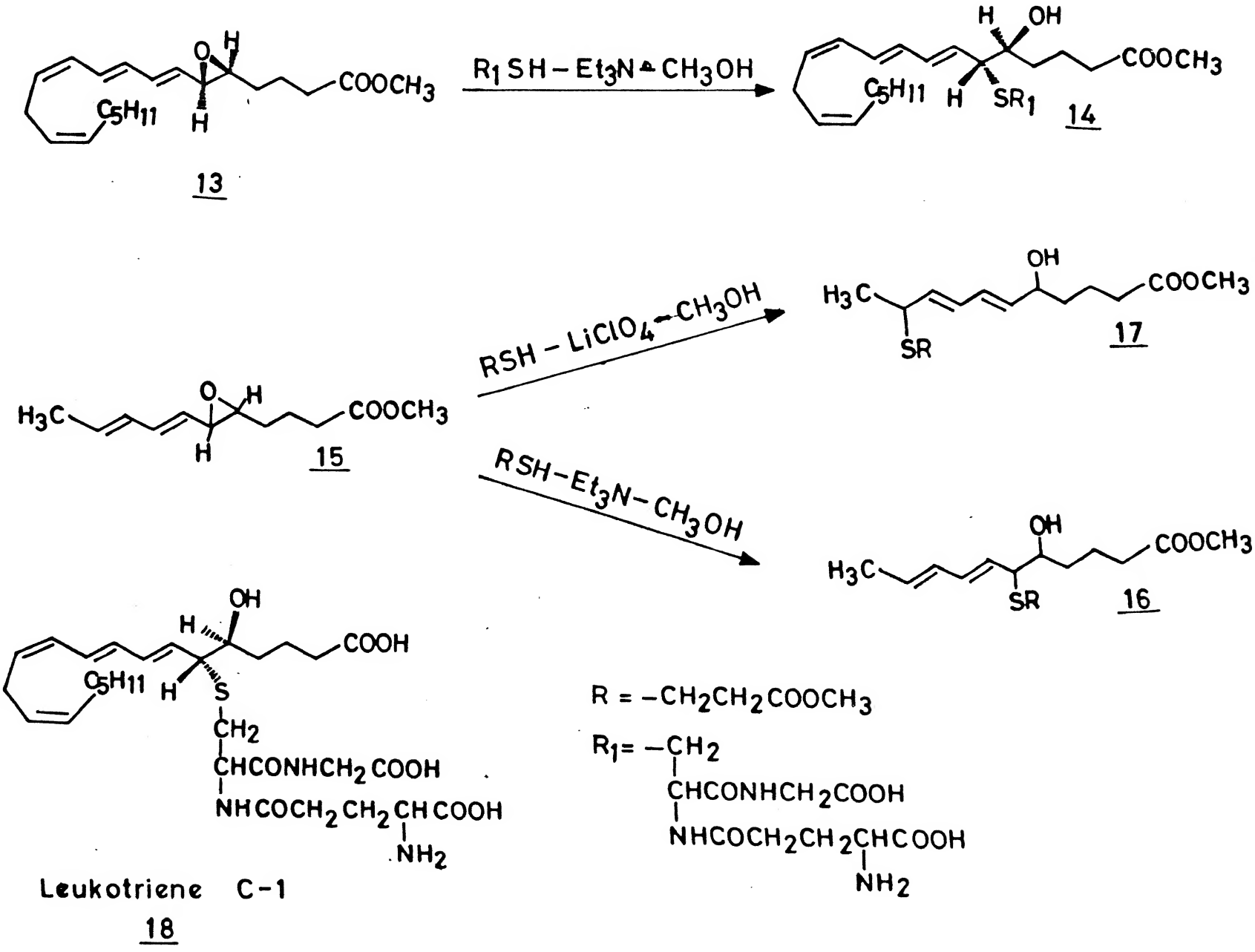

COOCH3
C5H11
R1SH – Et3N – CH3OH
OH
SR1
14
13
RSH – LiClO4 – CH3OH
H3C
SR
17
15
RSH – Et3N – CH3OH
16
COOH
CH2
CHCONHCH2COOH
NHCOCH2CH2CHCOOH
NH2
Leukotriene C-1
18
R = –CH2CH2COOCH3
R1= –CH2

Figure 4

the stereochemistry of the resulting double bond depends on the particular reaction condition chosen[9].

Corey et al.[10] have developed reaction conditions to afford 1,2 or 1,6 addition of sulphur nucleophiles to monoepoxides **13** and **15** (Fig. 4). Reaction of **13** in a minimum of methanol with a variety of sulphydryl compounds and triethylamine results **14** the 1,2 adduct. The epoxy ester **15** with RSH-Et_3N-CH_3OH exclusively gives the 1,2 adduct **16** whereas the reaction with RSH-$LiClO_4$-CH_3OH yields **17**, the 1,6 adduct. This methodology is used in leukotriene **18** synthesis.

Vinyl epoxides undergo reduction reactions with metal hydrides and certain metal halides. A vinyl substituted β-hydroxy carbanion synthon[11] is produced by reduction of 1,3 diene monoepoxide **11** (Fig. 5) with $CrCl_2$ in the presence of LiI which reacts with aldehydes to afford **20** (R,R) adduct stereoselectively.

Functionalized vinyl epoxides have been found to undergo facile reductive ring opening with samarium diiodide[12] in THF in the presence of a proton source to provide (E) allylic alcohols **23** (Fig. 5).

Reduction of vinyl epoxides with metal hydrides[13] shows different selectivity towards different reducing agents. The vinyl epoxide **24** (Fig. 5) with DIBAH (diisobutyl aluminum hydride) affords **25** (Fig. 5), the 1,4 adduct. But with AlH_3 it gives the carbinol **26** from which the pheromone sitophilure **27** (Fig. 5) can be obtained.

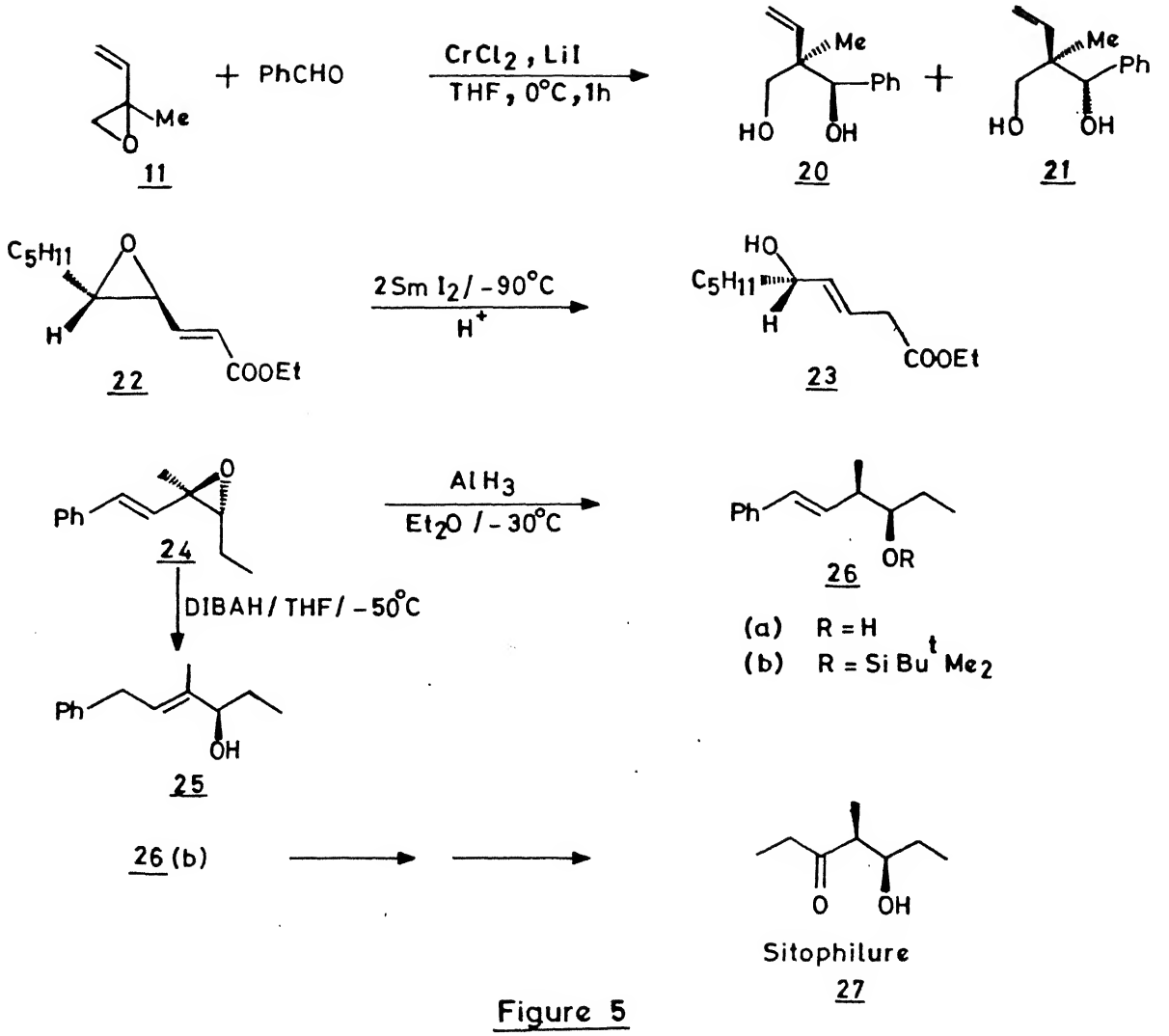

+ PhCHO
CrCl2 , LiI
THF , 0°C , 1h
Me
Ph
HO
OH
11
20
21
C5H11
H
COOEt
22
2Sm I2 / -90°C
H+
23
Ph
24
AlH3
Et2O / -30°C
OR
26
DIBAH / THF / -50°C
25
(a) R = H
(b) R = Si Bu t Me2
26 (b)
O
Sitophilure
27

Figure 5

In literature, it is mentioned that vinyl epoxides undergo intramolecular nucleophilic additions. Stork[14] et al. have developed a method where intramolecular opening of a trans disubstituted epoxide by a carbanion leads to a cyclohexane ring **29** (Fig. 6) rather than a cyclopentane ring.

Formation of substituted oxepanes **31** and **32** via intramolecular opening of vinyl epoxides by 'oxygen' nucleophiles has been reported by Nicolaou et al.[15]. Interestingly the reaction takes place by activation of 7-endo over 6-exo hydroxy epoxide opening (Fig. 6).

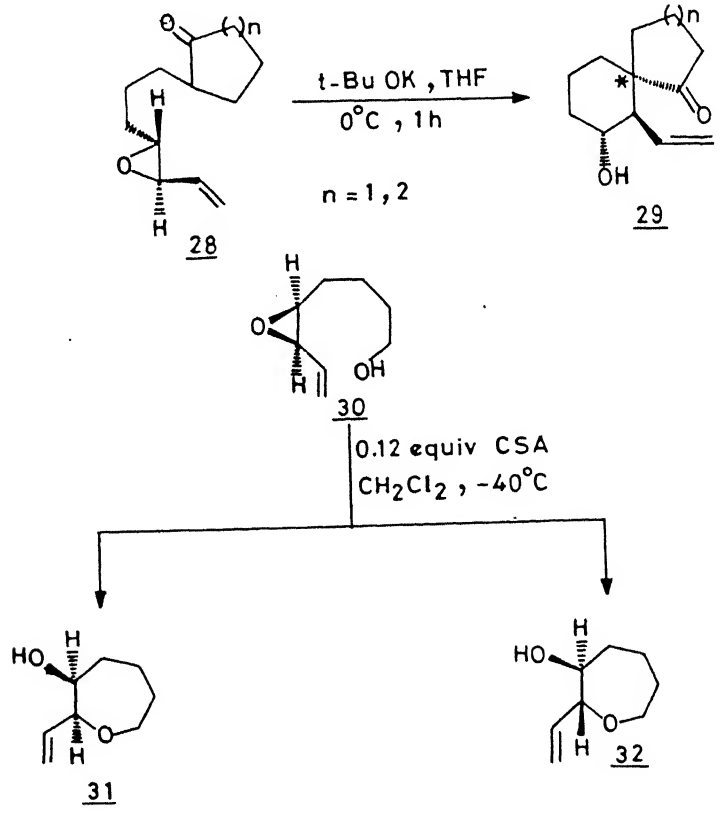


Figure 6

Reactions of cyclic as well as acyclic 1,3 diene monoepoxides with a variety of organometallic reagents have been

reported in the literature. Attempts have been made to get selectively 1,2 or 1,4 adduct in various ways. Cuprate reagents[16,17] favour the formation of 1,4-addition products to afford **35** (with the 'E'-isomer predominating) (Fig. 7).

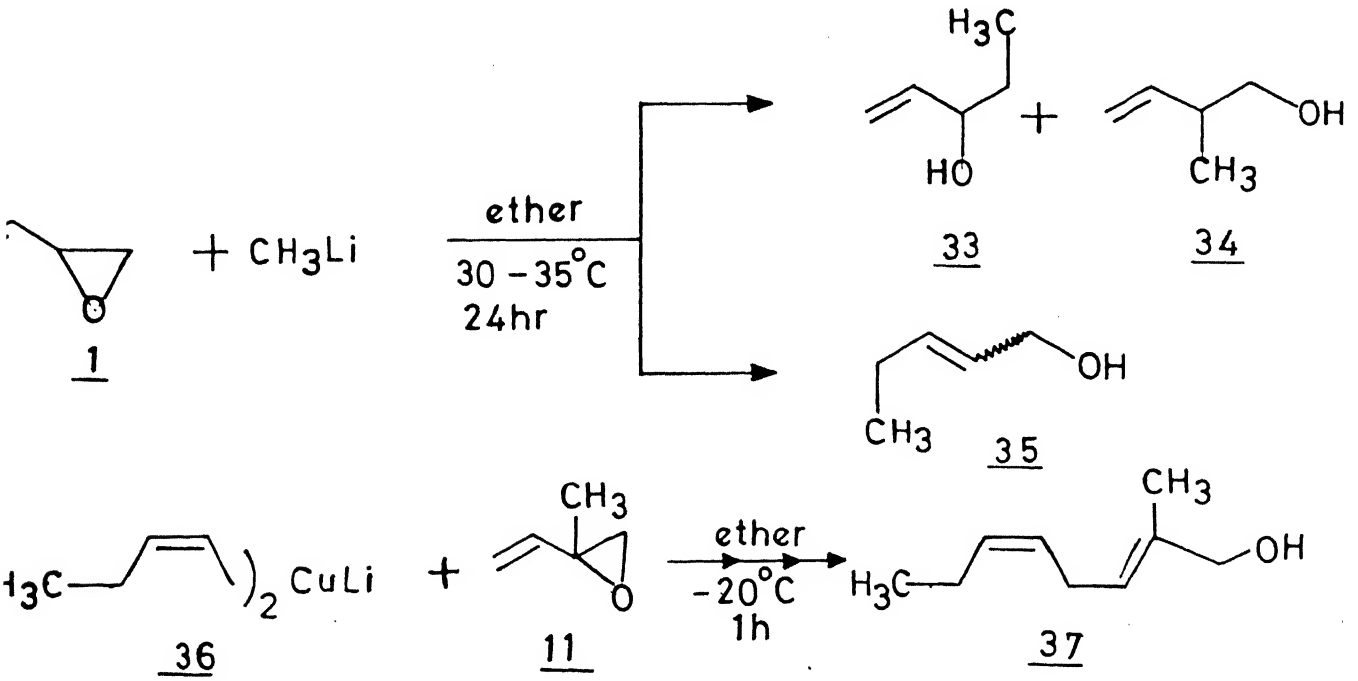


Figure 7

Synthesis of unsymmetrical 2,5 alkadienol **37** (Fig. 7) has been accomplished by the reaction of olefinic organocopper reagents with isoprene epoxide[18]. This dienol is a useful synthon for the preparation of some pheromones.

Direct 1,2 addition at the secondary end of the epoxide to afford **34** (Fig. 7) is usually favored by the use of organomagnesium reagents[16,17,26].

Marino[19] et al. have reported the reactions between dialkylcuprate and cyclic monoepoxides of 1,3 diene. They have observed a very useful regiospecific reaction with the monoepoxide **38** (Fig. 8). Much work[20-22] has been done with cyclohexane system. But the lack of regiospecificity in the cyclohexene epoxide **5** system renders the approach of

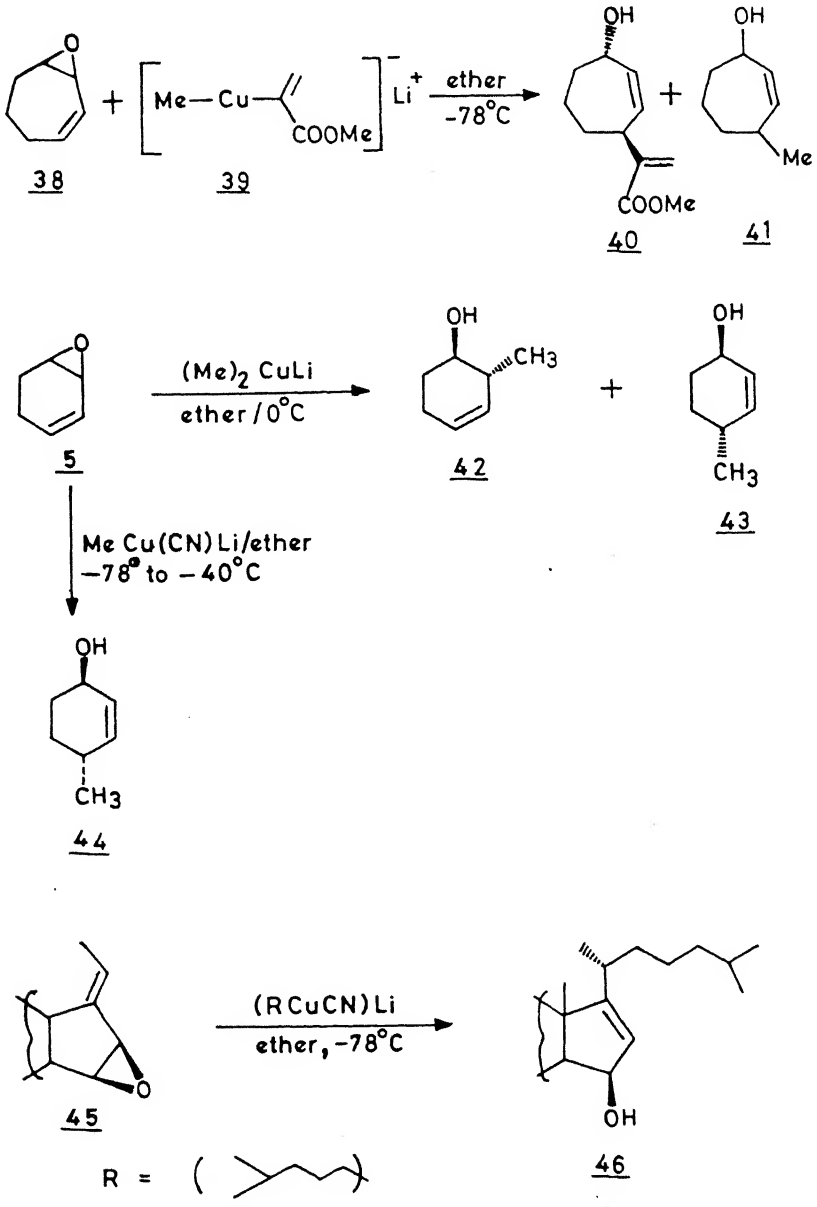


Figure 8

dialkylcuprate synthetically impractical. Both 1,2 and 1,4 adducts (**42** and **43**: Fig. 8) are obtained[20] with complete trans stereospecificity in this case. On the other hand with mixed cyanocuprate[23,24] reagents stereo (100% trans) and regiospecific (1,4 adduct > 95%) addition to the cyclohexene epoxide is observed (**44** Fig. 8). This methodology is extended to a chiral alkylidene oxirane[25] of known configuration and two asymmetric centres were generated in a 1,4 relationship (**46** Fig. 8).

Naruta[27] and coworkers have developed a method where both cyclic and acyclic vinyl epoxides successfully gave 1,2 adduct, (**51, 52, 53** in Fig. 9). For this purpose allyl stannanes

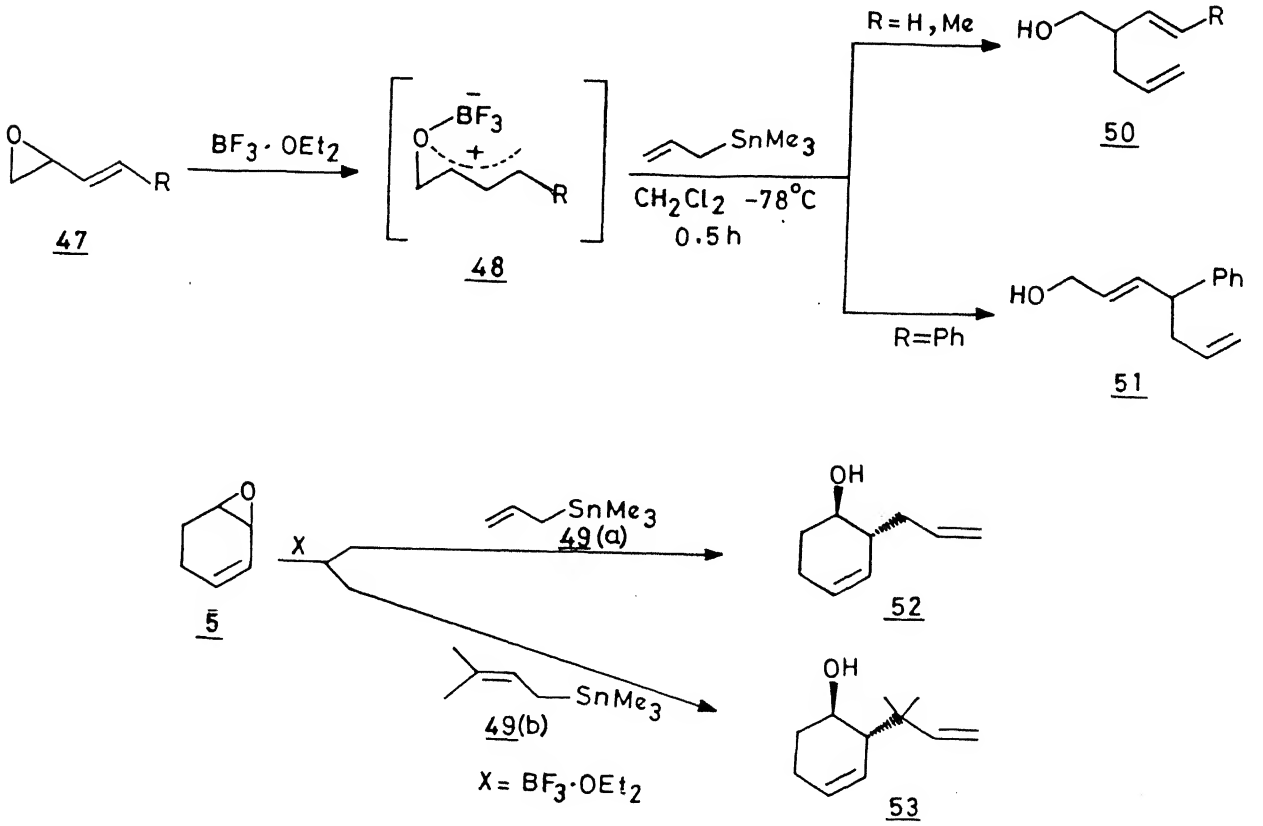


Figure 9

have been used in the presence of a Lewis acid. This method is used in the synthesis of a polyprenyl alcohol.

There are some examples where vinyl epoxides react with nucleophiles to give 1,4 or 1,2 adduct in presence of Pd (0), as a catalyst. Three examples are shown in Fig. 10.

Tsuda[28] used ketoacids as nucleophile (**57**: Fig. 10) and 1,4 adduct **58** is obtained. Trost[29] has used alcohols as nucleophilic partners. He used stannylether **60** for the -allyl intermediate and 1,2 adduct **61** is obtained. Recent interest in amino sugars has drawn attention to the process of hydroxyamination. The ready availability of epoxides in enantiomerically pure form from olefins makes such intermediates particularly useful in achieving a net hydroxyamination of olefins. Trost[30,31] and coworkers have used aryl isocyanate for the trapping of the initial zwitterion from vinyl epoxide in presence of Pd (0) to get thermodynamically more stable 2-oxazolidones **62** (Fig. 10). These oxazolidones finally give the aminoalcohol derivatives of defined stereochemistry and this has led to the synthesis of (-) acosamine **64** (Fig. 10).

Recently Oshima et al.[32] have studied Et_3B induced radical reaction of vinyl epoxide **1**. Intramolecular radical cyclisations have also been realised by them to obtain carbocyclic compounds **68** and **69** (Fig. 11). Likewise Feldman et al.[33] have synthesised polysubstituted tetrahydrofuran **72** via free radical mediated (3 atoms + 2 atoms) addition of functionalized alkenes to aryl vinyl epoxide **70** (Fig. 11) in the presence of diphenyl disulfide.

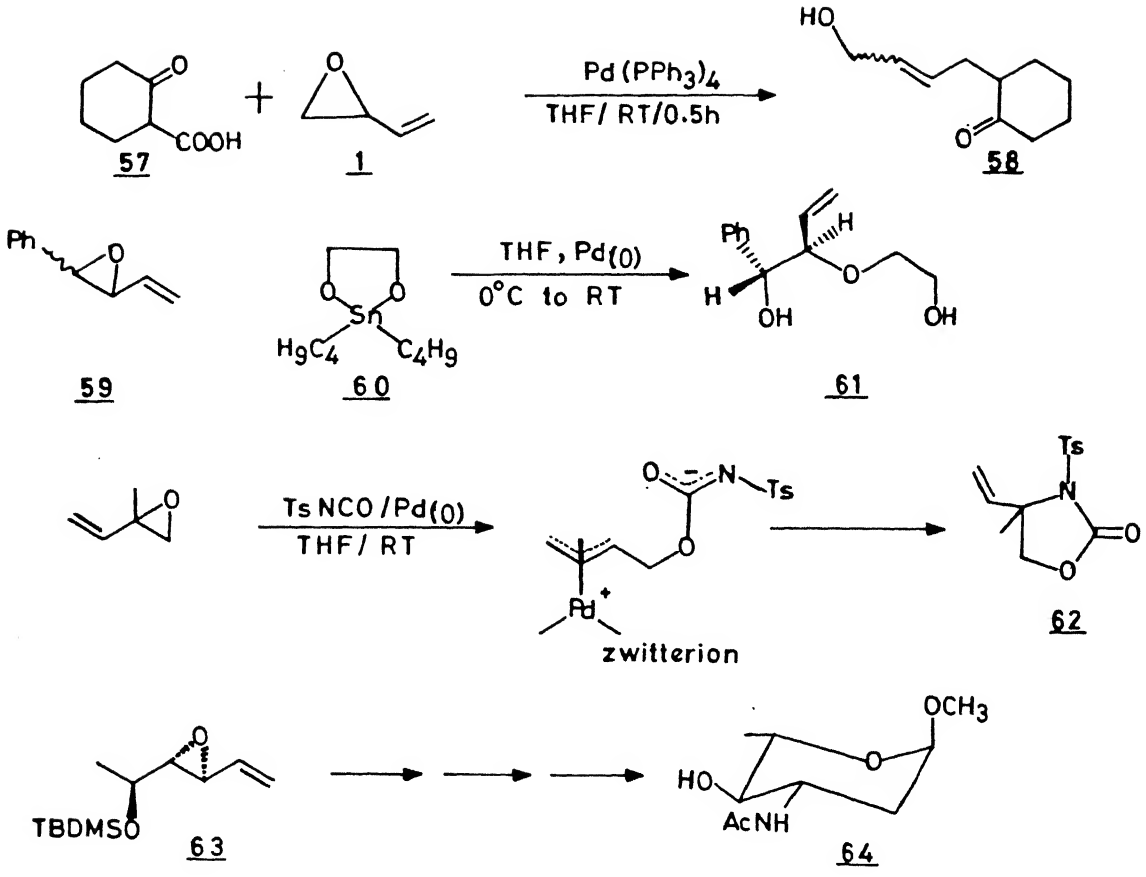

COOH
57
1
Pd(PPh3)4
THF/ RT/0.5h
HO
O
58
Ph
O
59
O
Sn
O
H9C4
C4H9
60
THF, Pd(0)
0°C to RT
Ph
H
OH
H
O
OH
61
O
TsNCO/Pd(0)
THF/ RT
O
N
Ts
O
Pd+
zwitterion
Ts
N
O
O
62
TBDMSO
O
63
OCH3
O
HO
AcNH
64

Figure 10

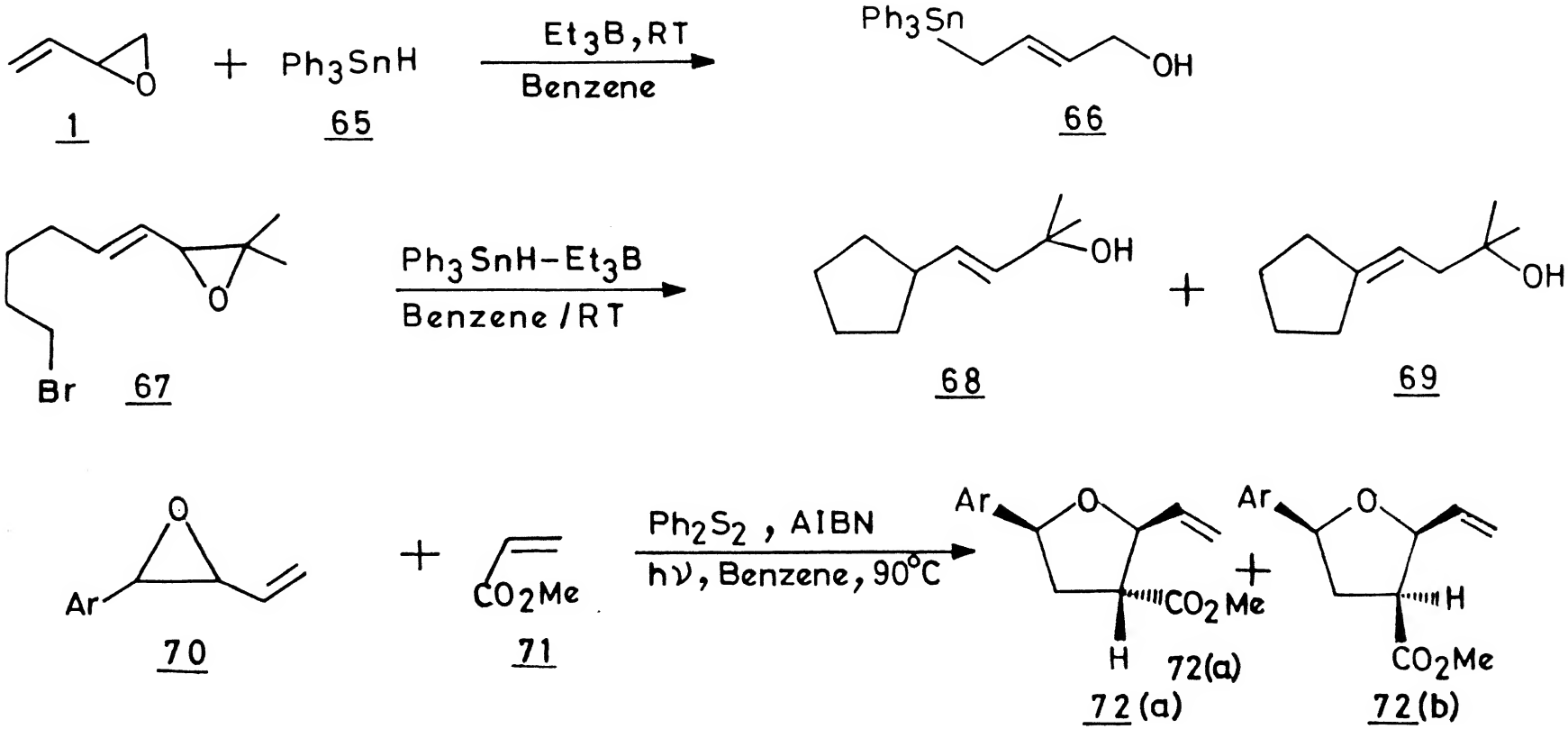

Et3B, RT
Benzene
Ph3SnH
Ph3Sn
OH
1
65
66
Ph3SnH–Et3B
Benzene / RT
Br
67
68
69
Ar
70
CO2Me
71
Ph2S2 , AIBN
hν, Benzene, 90°C
H
72(a)
72 (a)
72 (b)

Figure 11

Rearrangement of vinyl epoxides to obtain dihydrofuran system **73b** (Fig. 12) has been reported by Hudlicky et al.[34].

Most recently in the synthesis of a β-lactone esterase inhibitor i.e. valilactone[35], the key reaction involved the conversion of a chiral vinyl epoxide to π-allyl-tricarbonyliron complex and its selective oxidation to β-lactones **76** with good stereochemical control (Fig. 12).

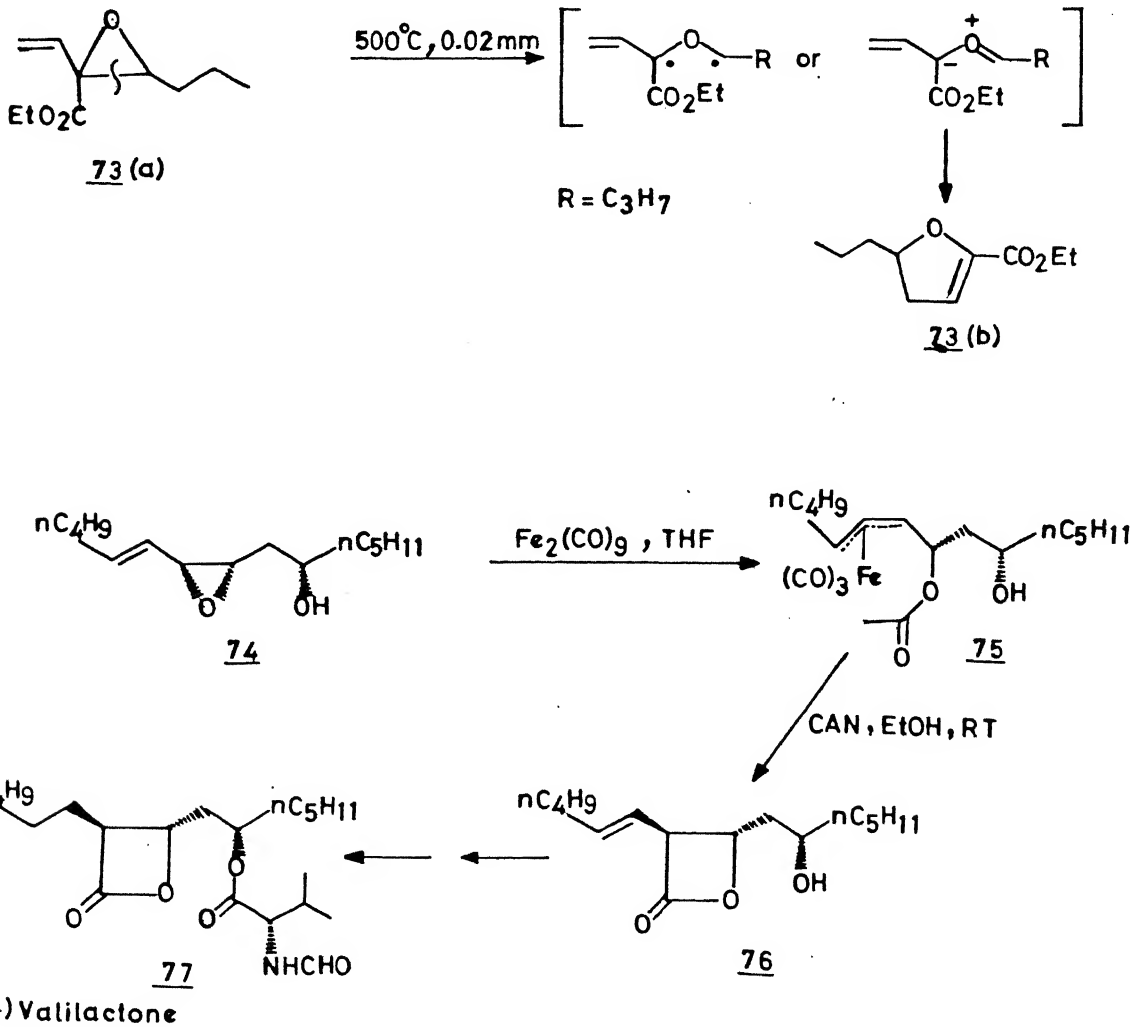


Figure 12

I.2 Synthesis of Vinyl Epoxides

Importance of vinyl epoxides as useful intermediates in organic synthesis has been discussed above. Literature survey reveals that there are a number of approaches towards the synthesis of vinyl epoxides. Various approaches of these syntheses could be divided into three categories. These are delineated in Fig. 13.

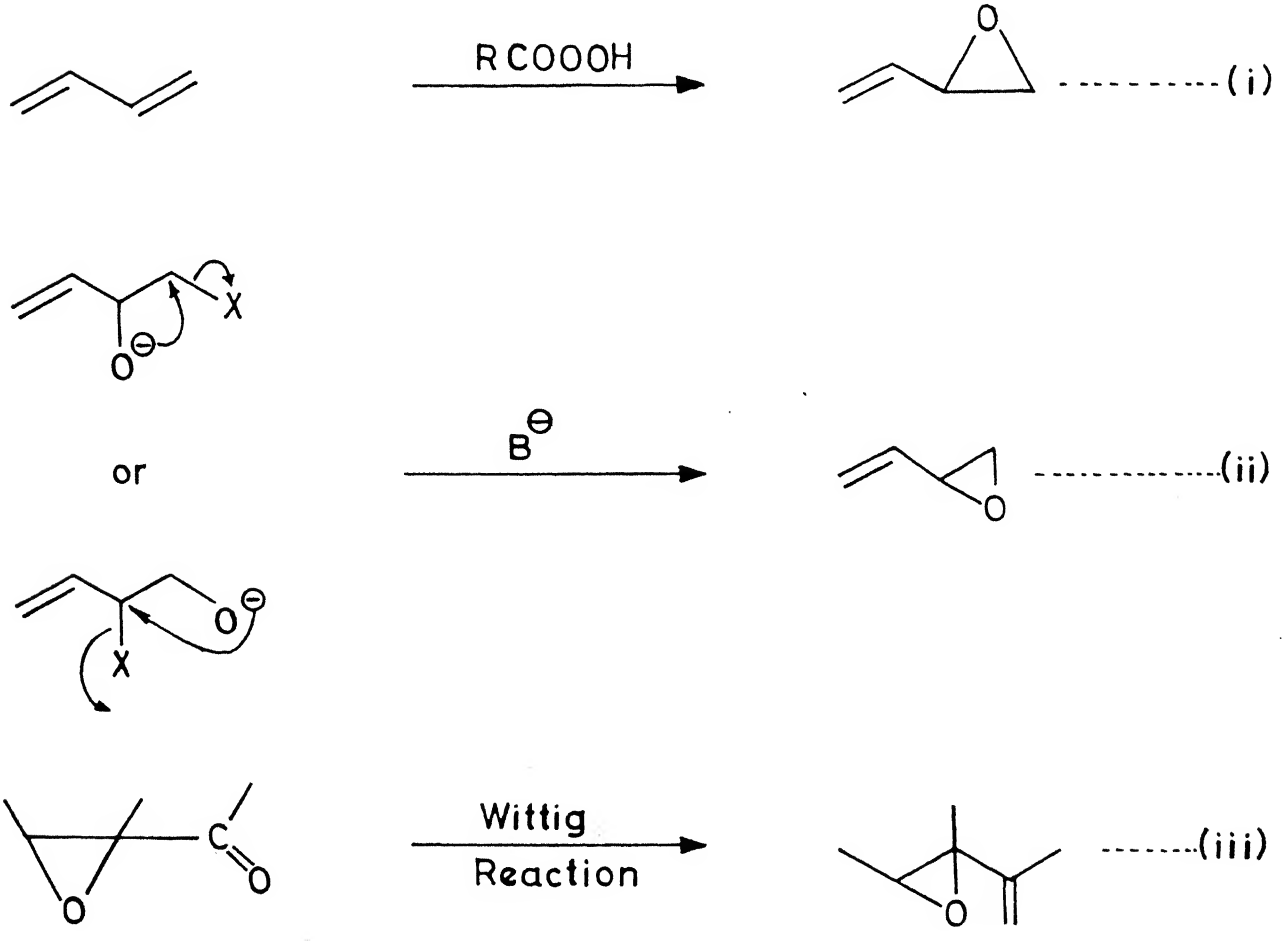


Figure 13

Equation (i) deals with one of the most obvious reactions viz. monoepoxidation of 1,3 dienes. An example of this type is the epoxidation of cyclopentadiene[36] with peracetic acid in the presence of Na_2CO_3 giving 3,4 epoxy cyclopentene **78** (Fig. 14) in 75% yield. Addition of Na_2CO_3 apparently is required to neutralise acetic acid formed in the reaction. The epoxide, otherwise, reacts with acetic acid. This method has been quite useful in the synthesis of other vinyl epoxides[37]. In addition to peracetic acid other peracids such as perbenzoic acid and perphthalic acid[38] have also been employed for the synthesis of vinyl epoxides.

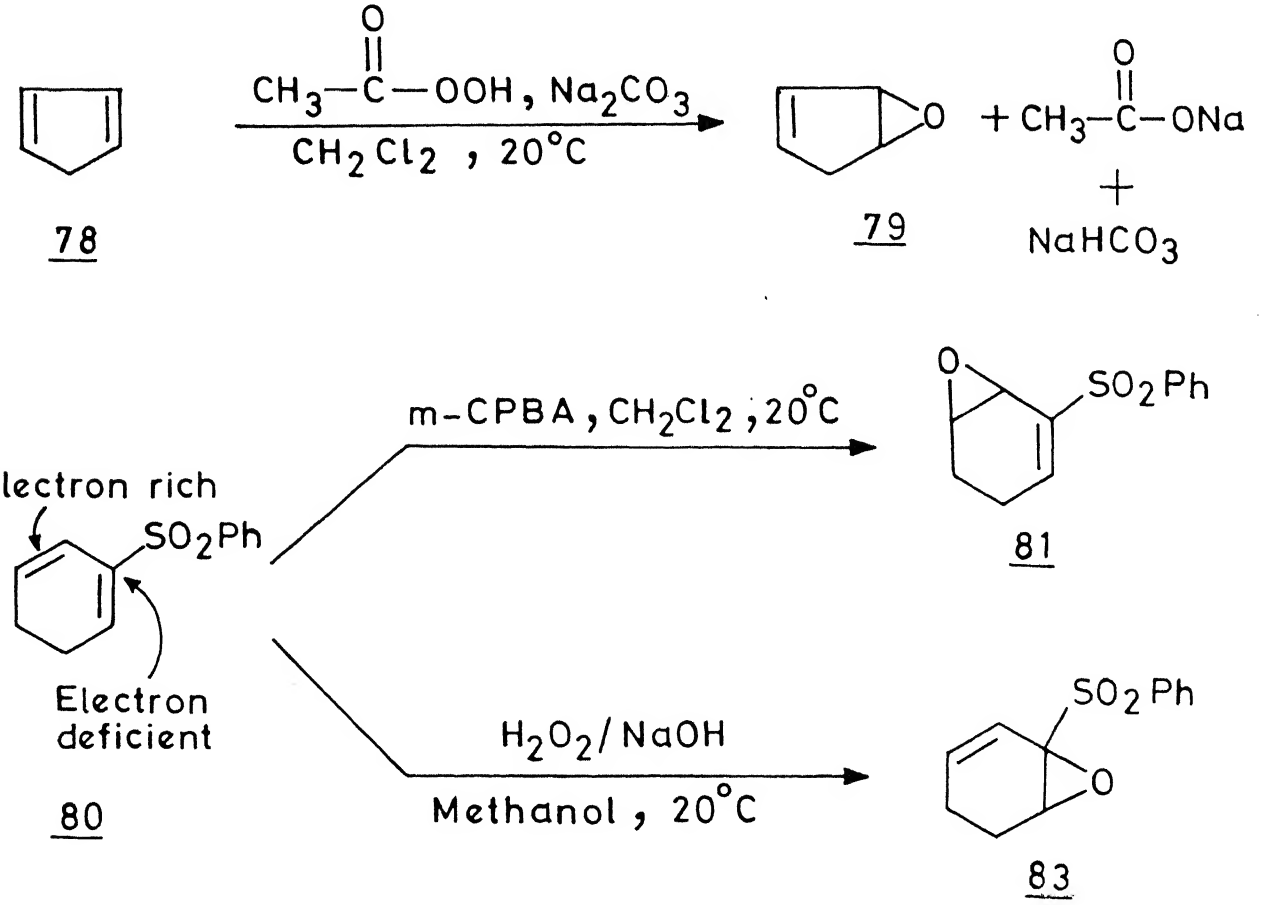
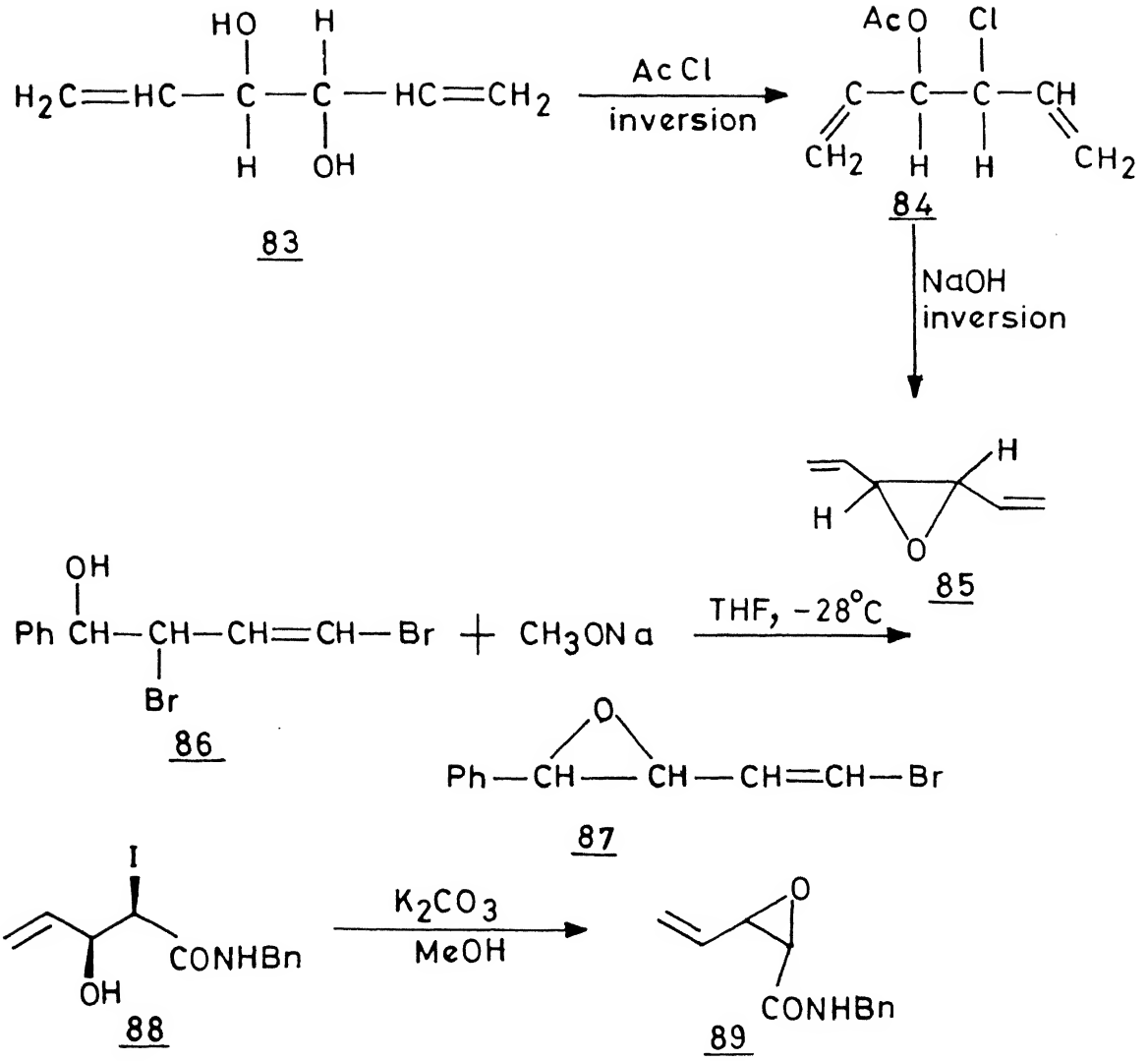


Figure 14



83 84 85 86 87 88 89

Figure 15

Vinyl epoxides from 1,3 dienes having an electron withdrawing group on one of the double bonds have also been synthesised. Depending on the method of epoxidation either of the double bond is epoxidised. Thus e.g. 2- (phenylsulphonyl)-1,3 cyclohexadiene **80** upon reaction with m-chloroperbenzoic acid selectively epoxidises the 3,4 double bond to form 3,4 epoxy-2-(phenylsulphonyl)-1-cyclohexene **81**. On the other hand with H_2O_2/NaOH the other double bond is epoxidised to give **82**[39] (Fig. 14). Likewise synthesis of 3,4-epoxy- 3 nitro-1- alkenes has also been reported in the literature[40].

The second approach as shown in eqn (ii) fig. 13 involves treatment of vicinal halohydrin[34, 41-43] with a base. In place of halogen many other leaving groups such as -OTs[13,44] and -OMs[45] have also been utilised. A few examples are shown in Fig. 15 and fig. 16.

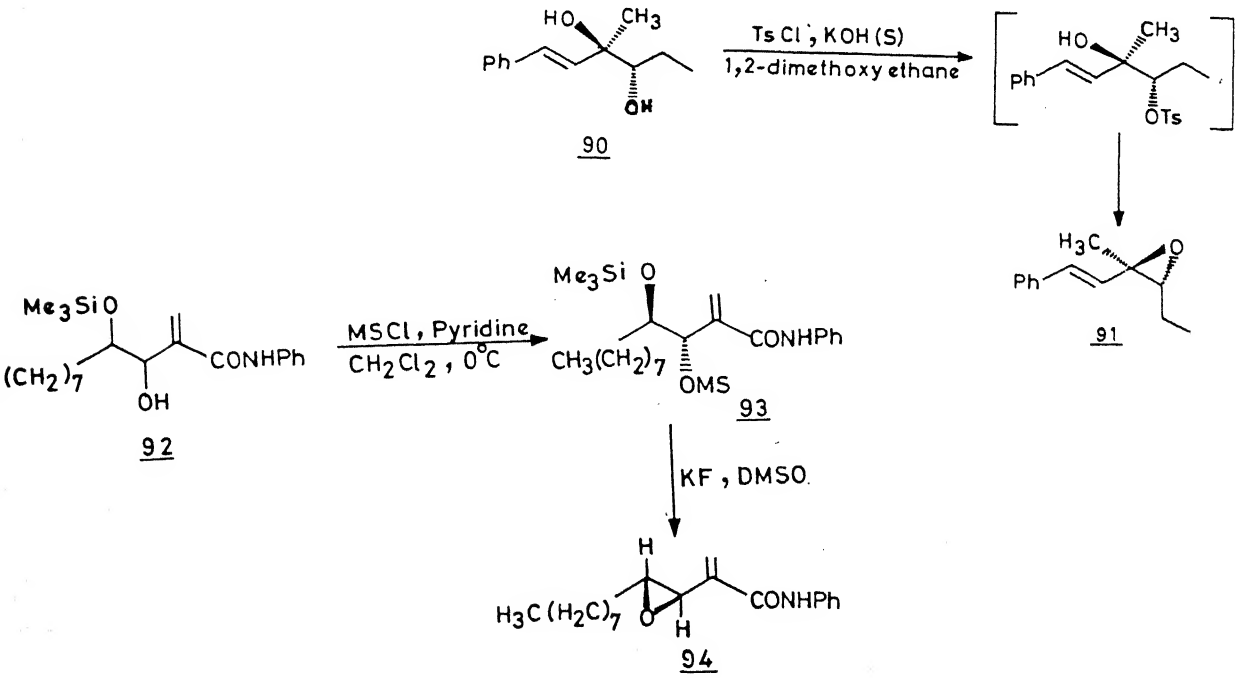


Figure 16

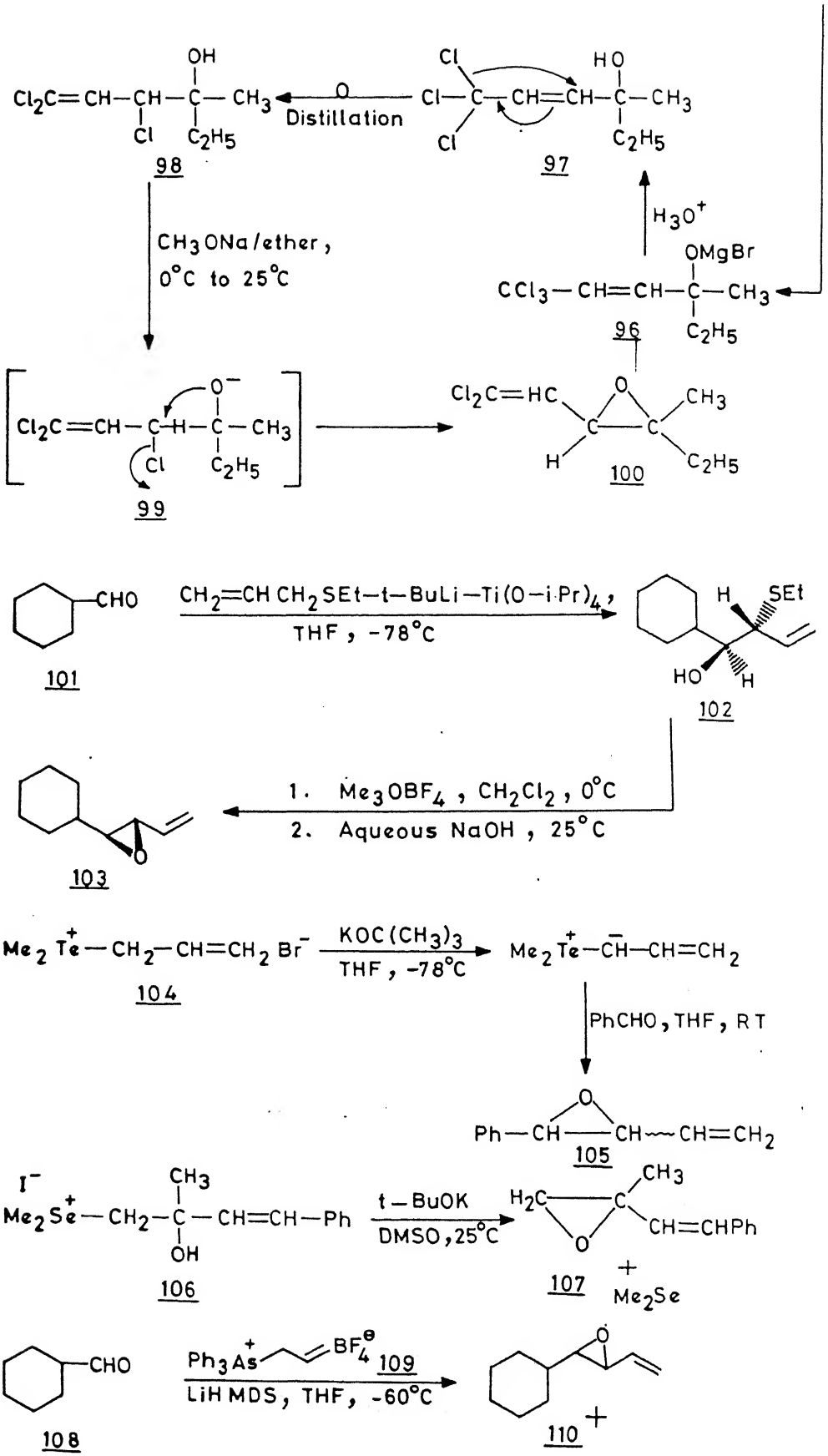

Distillation
98
97
96
99
100
CH3ONa/ether,
0°C to 25°C
H3O+
101
102
103
1. Me3OBF4, CH2Cl2, 0°C
2. Aqueous NaOH, 25°C
104
105
106
107
108
109
110
THF, -78°C
PhCHO, THF, RT
t-BuOK
DMSO, 25°C
LiHMDS, THF, -60°C

Figure 17

An interesting extension of such an approach has been in the synthesis of certain vinyl epoxides, involving an allylic rearrangement[46] as shown in fig. 17.

In addition to the above mentioned leaving groups there are other groups derived from divalent sulphur[31,42(ii),47] tellurium[48] and selenium[49] and trivalent arsenic[50] compounds which act as excellent leaving groups in the form of the corresponding onium salts. A few representative examples of each of them are shown in Fig. 17.

In this category of reactions yet another interesting example is reported in the literature[51] which involves a series of reactions starting from propargyl bromide. This is shown in Fig. 18.

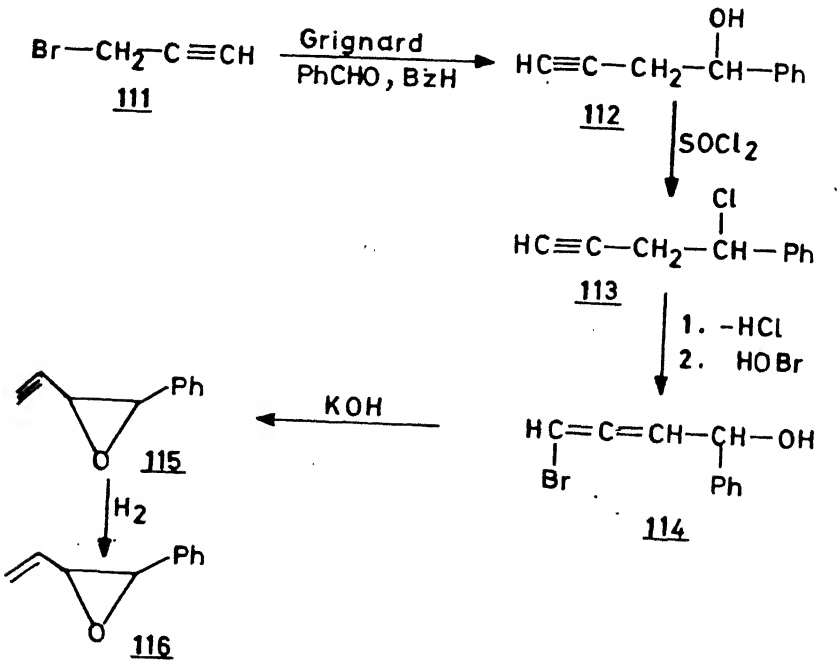
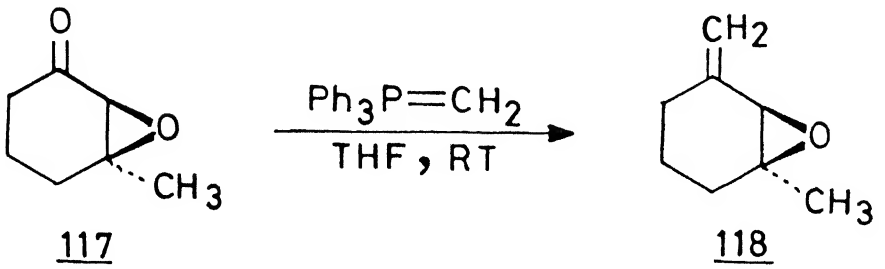


Figure 18

The third approach as shown in eqn. (iii) Fig. 13 is dependent on the Wittig reaction with the epoxycarbonyl compounds[10, 12, 14, 24] which in turn are derived from the corresponding α, β-unsaturated carbonyl compounds which are obtained from oxidation of allylic alcohols. One such example is shown in Fig. 19.



117 118

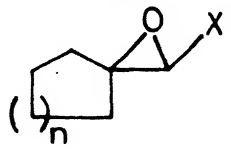
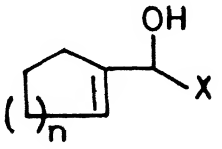
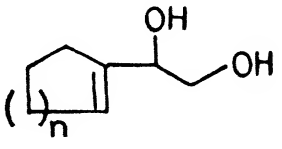
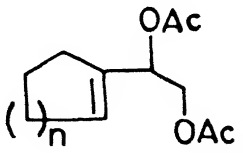
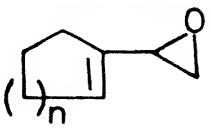
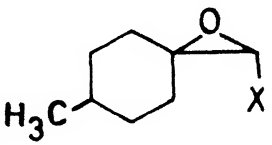
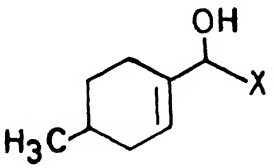
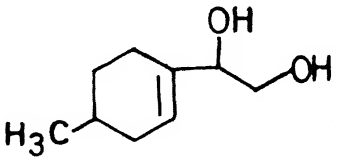
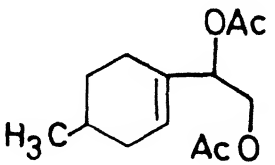
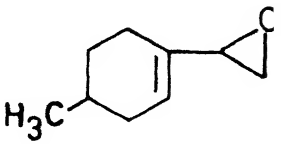
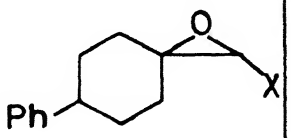
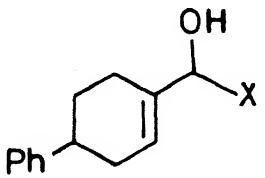
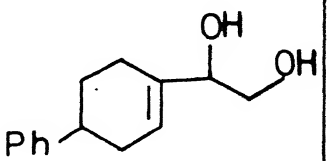
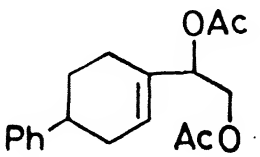
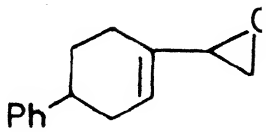
Figure 19

I.3 Results and Discussion

In the introduction part of this chapter importance of vinyl epoxides as useful intermediates has been described. Vinyl epoxides, which contain two functional groups viz., >C = C< and  , offer three sites for the reaction and various approaches for regioselective reactions on any one of these sites have been well studied in the literature[52]. Depending on the need of structural requirements various approaches towards their synthesis have been developed.

From our group, regioselective transformation of glycidic esters into α- hydroxy- β,γ -unsaturated esters using $BF_3.OEt_2$ (or $ClSiMe_3$) has been reported[53]. Ready accessibility of these geminal hydroxy esters suggested a possibility of converting them into vinyl epoxides via the approach as mentioned in eqn. (ii) (Fig. 13). Literature survey revealed that such types of vinyl epoxides have not been reported so far. Our approach towards the conversion of α- hydroxy- β,γ -unsaturated esters involved their reduction with $LiAlH_4$ to the corresponding vicinal diols. Treatment of these diols with p-toluenesulphonyl chloride in presence of pyridine gives the corresponding tosylates derived from the terminal hydroxy groups. These tosylates were used for the next step without purification. They were treated with sodium hydride to form the epoxide ring. This sequence of reactions is shown in Fig. 20. Various glycidic esters chosen for this study are shown in table I along with the hydroxy esters, the diols and the corresponding epoxides.

Conversion of glycidic ester into vinyl epoxide

Entry	Glycidic ester 118	Isomerised hydroxy ester 119	Diol 120	Diacetate 121	Vinyl epoxide 122
					
1	118a n = 1	119a n = 1	120a n = 1	121a n = 1	122a n = 1
2	118b n = 2	119b n = 2	120b n = 2	121b n = 2	122b n = 2
3	118c n = 3	119c n = 3	120c n = 3	121c n = 3	122c n = 3
4	 118d	 119d	 120d	 121d	 122d
5	 118e	 119e	 120e	 121e	 122e

X = $-COOC_2H_5$

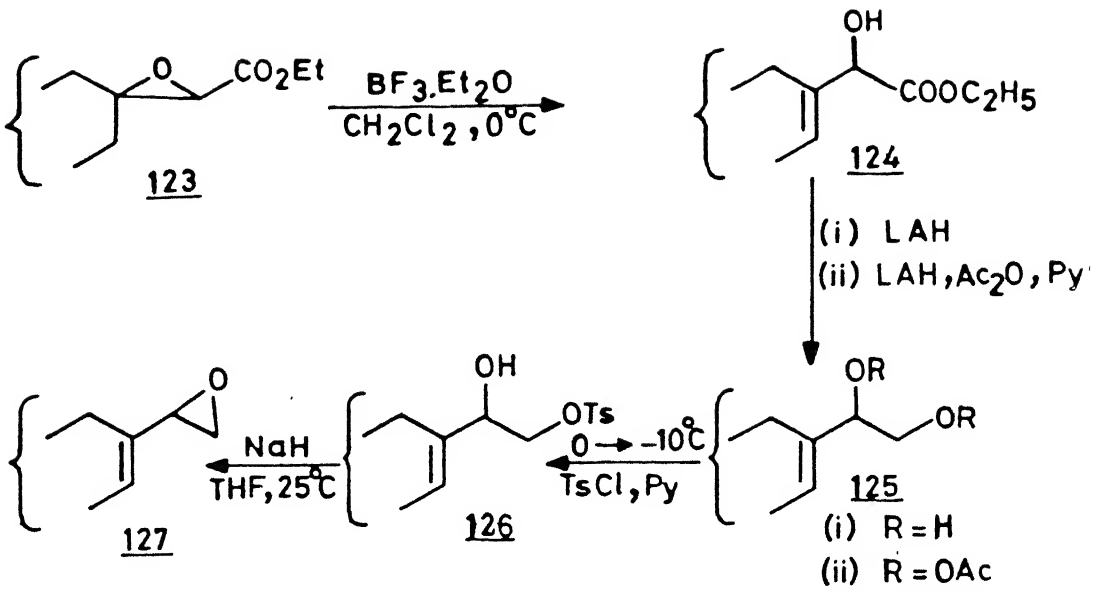


Figure 20

The glycidic esters **118 (a-e)** were synthesised according to the literature[54] procedure. Surprisingly the glycidic esters from 4-methylcyclohexanone and 4-phenylcyclohexanone are not known in the literature and they were prepared by following the same standard literature[54] procedure. The diols obtained upon reduction of the hydroxy-esters were characterised as the corresponding diacetates. Spectroscopic details of all of these hydroxy esters, the diols and the corresponding diacetates are given in the experimental part. The vinyl epoxides in each case displayed a characteristic triplet around 3.0-3.38 with a coupling constant of 3-4 Hz for the vinylic methine located at the epoxy carbon. Further spectroscopic details for vinyl epoxides are mentioned in the experimental part.

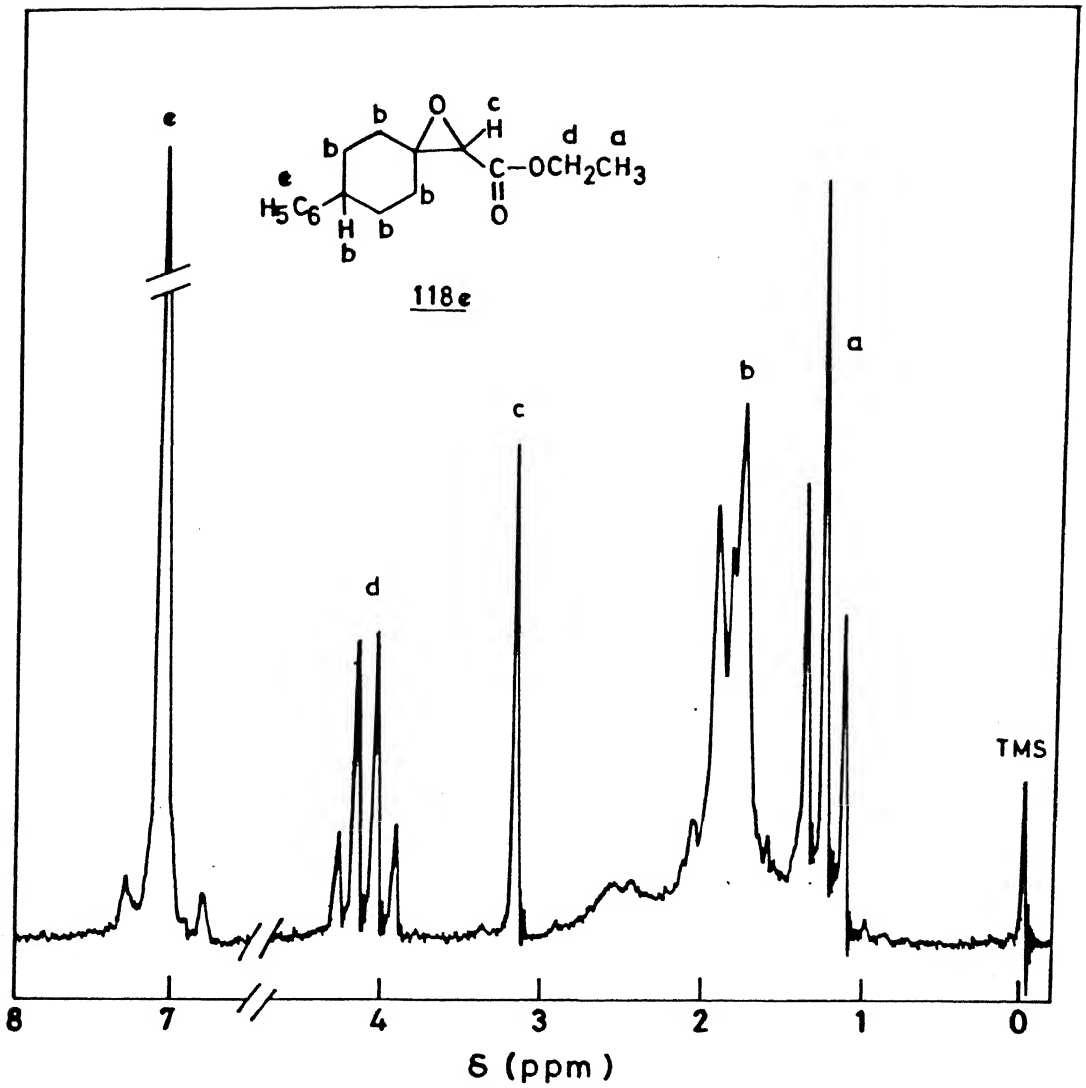


Figure I.1: ^{1}H NMR spectrum (60 MHz) of **118e**

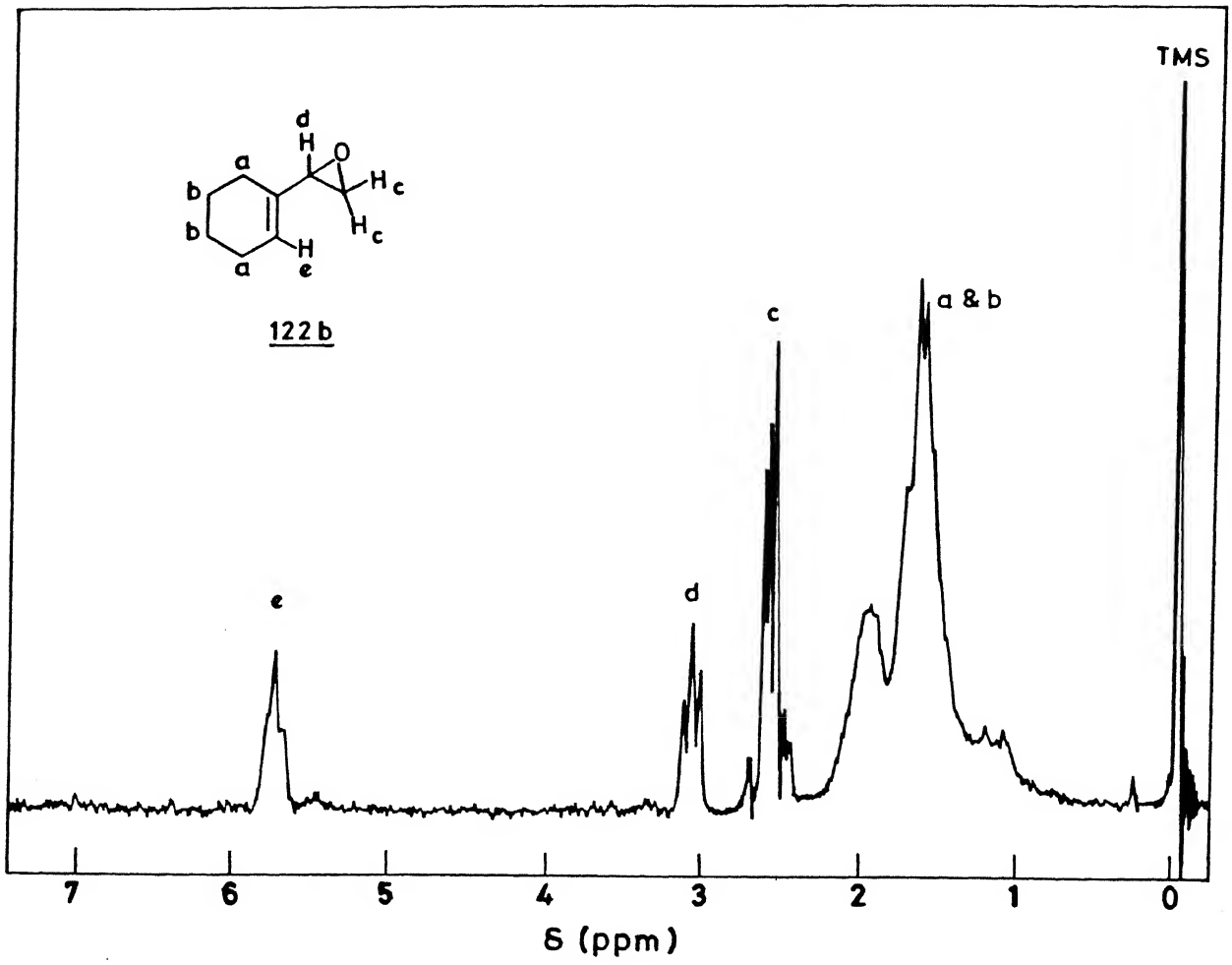


Figure I.2: ^{1}H NMR spectrum (60 MHz) of **122b**

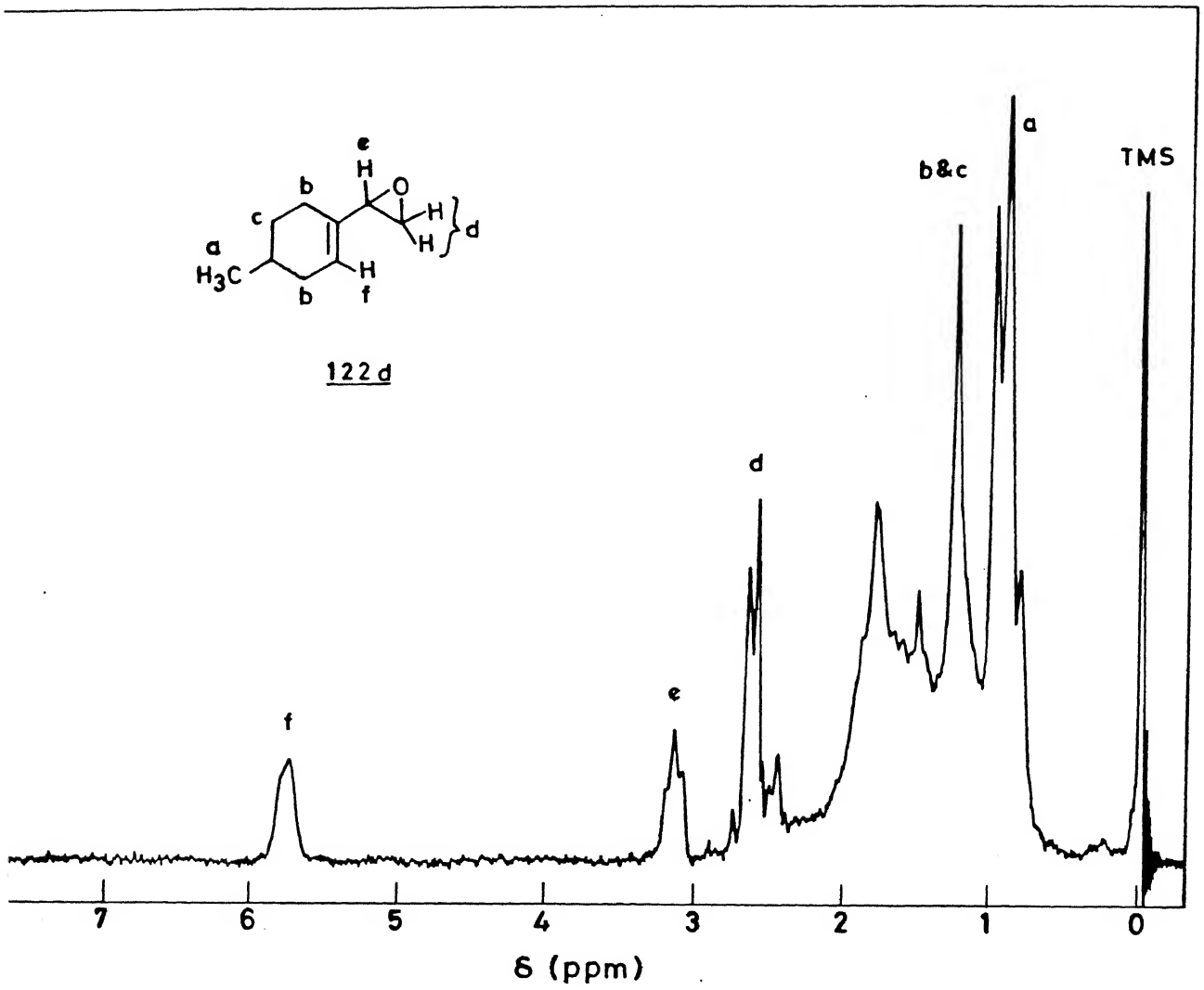


Figure I.3: ^{1}H NMR spectrum (60 MHz) of **122d**

Since many of the biologically and medicinally important compounds show their activities in only one of the optical antipodes it is necessary that different methods should be developed to synthesise a variety of intermediates in optically pure form. It was, therefore, felt that if these vinyl epoxides of type **127** are obtained in optically pure form it would be an interesting and useful study. From the above described results it is evident that vinyl epoxides possessing structures of type **127** could be easily procured from the corresponding glycidic esters albeit in racemic forms.

Literature survey shows that syntheses of chiral vinyl epoxides are based on three methodologies. These are (i) starting from a chiral compound, (ii) using a chiral catalyst and (iii) via resolution of (±) racemic compounds.

One example is given in the following discussion based on method (i) i.e. chiron approach.

Corey et al[10] have synthesised the chiral vinyl epoxide **130** from 2, 3, 5-tribenzoyl derivative of D-(-) ribose, which leads to the chiral epoxy aldehyde **129** in seven steps.

The chiral epoxy aldehyde finally gave the chiral vinyl epoxide **130** (Fig. 21) which is used in the biosynthesis of leukotriene C-1.

The second methodology involves the use of chiral catalyst. In this method prochiral starting material undergoes enantioselective reaction with the help of chiral catalyst and enantiomerically pure chiral compound is obtained.

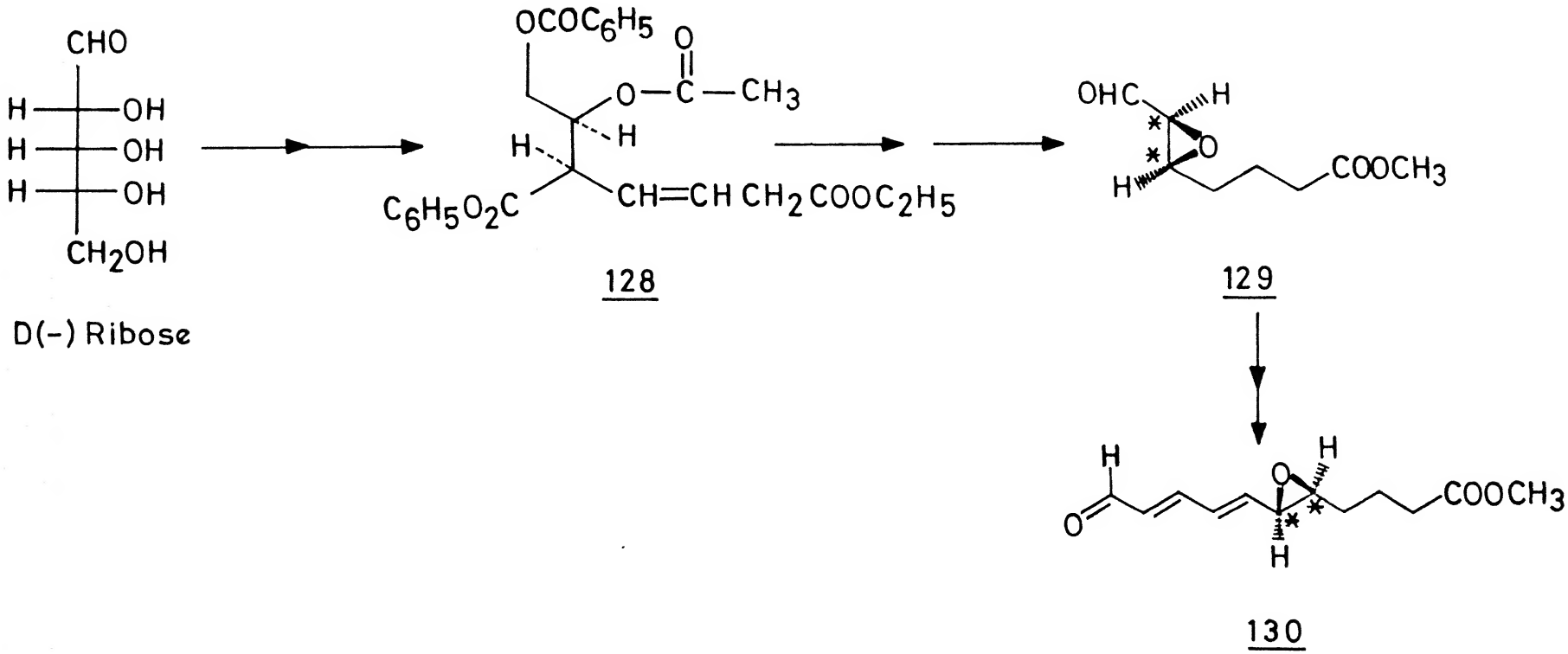

CHO
H—OH
H—OH
H—OH
CH2OH
D(-) Ribose
OCOC6H5
O
O—C—CH3
H
H
C6H5O2C
CH=CH CH2COOC2H5
128
OHC
H
O
H
COOCH3
129
H
O
H
O
H
COOCH3
130

Figure 21

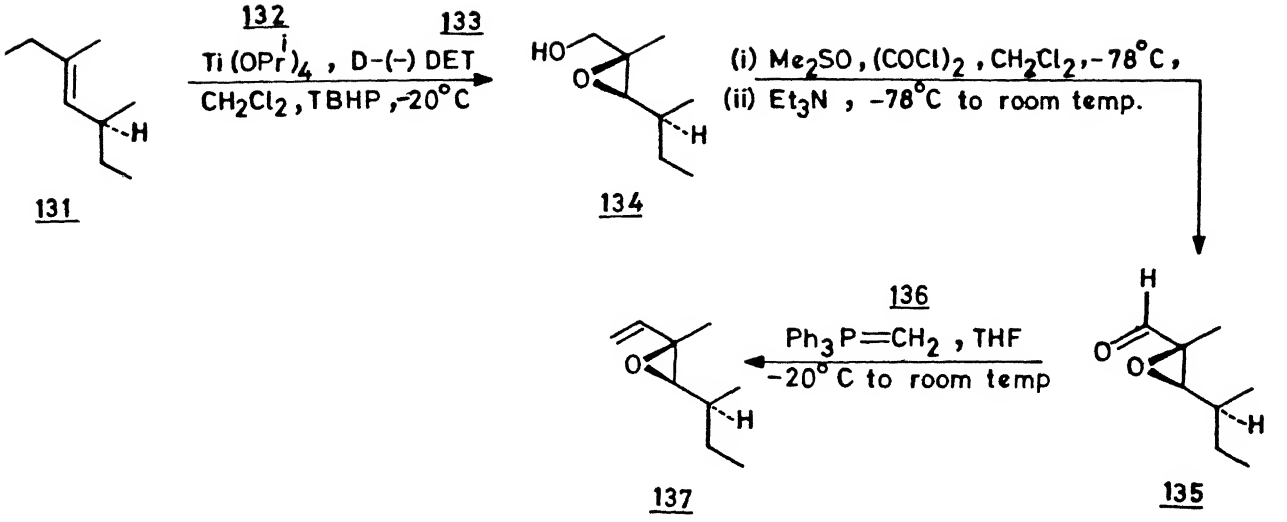
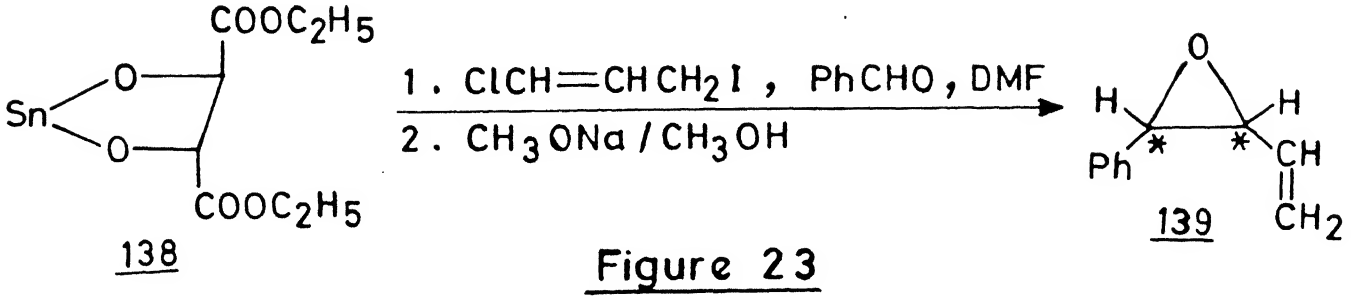


Figure 22

Combined with the Sharpless epoxidation[56] reaction, Swern oxidation[57] and Wittig or Horner-Emmons chemistry[58,59], would allow ready access to chiral, nonracemic vinyl epoxide[10,12,14,30,60]. In the Sharpless asymmetric epoxidation process prochiral alcohols have been epoxidised with TBHP-Ti(OPr^i)$_4$ and either (+) or (-) dialkyl tartarate to furnish enantiomerically pure epoxy alcohols (Fig. 22).

Asymmetric induction is also possible using chiral tin(II) alkoxide. Auge and Bourleaux[61] prepared and isolated tin(II)

diethyl tartarate which was used as a chiral catalyst to prepare optically active vinyl epoxide **139** (Fig. 23).



138 139

Figure 23

Bates et al.[35] have synthesised chiral vinyl epoxide using a cyclic sulphate (**141**) as a chiral catalyst. This catalyst enantioselectively introduces a chiral centre in the trimethylsilyl acetylene (**140**) which after a series of reactions gives the chiral epoxide **144** (Fig. 24).

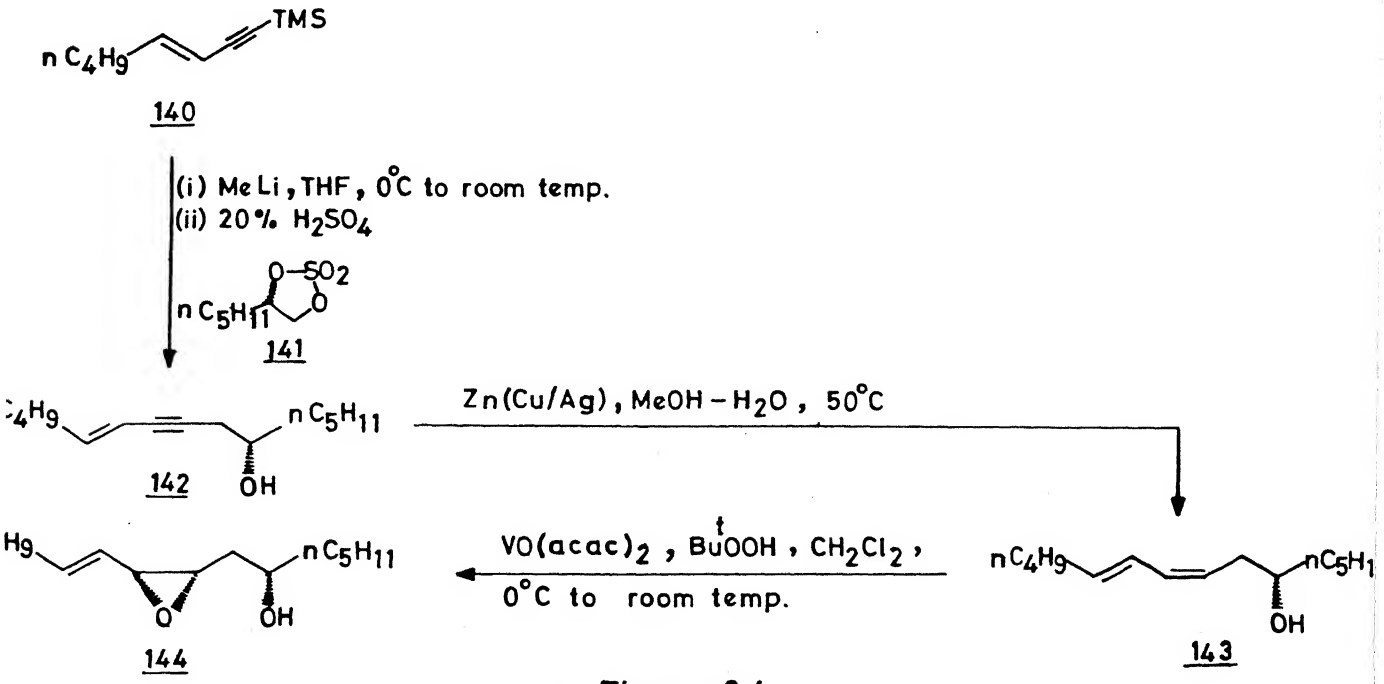
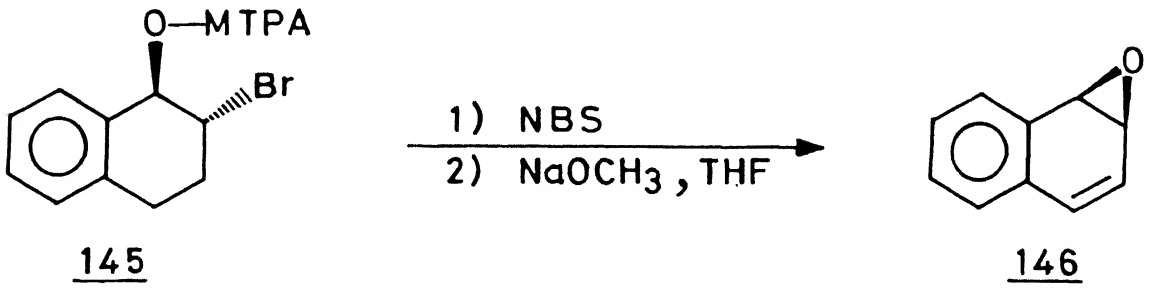


Figure 24

The third method involves the resolution of racemic precursors to get chiral vinyl epoxides. Efficient methods are available for the resolution of racemic alcohols to obtain chiral alcohol with high optical purity which can be converted to chiral epoxide later. One such example is given below.

Racemic alcohol **145** was converted to the ester of (-)-(S)-α-methoxy-α-trifluoromethyl phenyl acetic acid (MTPA). The mixture of diastereomeric esters was purified and the ester thus obtained was converted to enantiomerically pure alcohol. This alcohol[62] was then transformed to chiral vinyl epoxide **146** (Fig. 25).



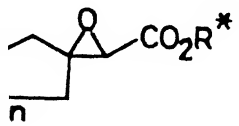
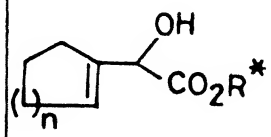
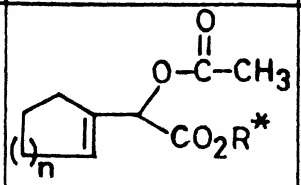
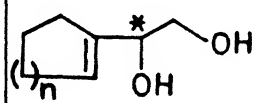
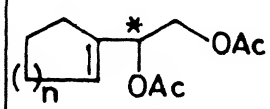
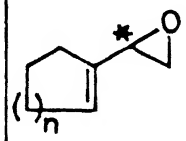
145 146

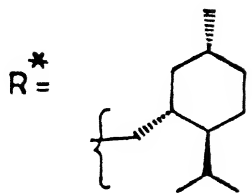
Figure 25

For the present study towards the synthesis of chiral vinyl epoxides we considered the possibility of starting our synthesis with glycidic esters in which the ester group is derived from the optically active menthol. It was anticipated that the menthyl group may exert an influence to discriminate between the two diastereomeric glycidic esters derived from (-) menthol. These

Table - II

Synthesis of Chiral Vinyl Epoxide

Glycidic ester 147 (a-c)	Hydroxy ester 148 (a-c)	Monoacetate ester 149 (a-c)	Chiral diol 150 (a-c)	Chiral diacetate 151 (a-c)	Chiral vinyl epoxide 152 (a-c)	$[\alpha]_D^{25}$
						
n =1 (147 a)	(148 a)	(149 a)	(150 a)	(151 a)	(152 a)	-1.23 (C1, $CHCl_3$)
n =2 (147 b)	(148 b)	(148 b)	(150 b)	(151 b)	(152 b)	-4.64 (C1, $CHCl_3$)
n =3 (147 c)	(148 c)	(149 c)	(150 c)	(151 c)	(152 c)	-5.48 (C1, $CHCl_3$)

R* = 

(1R, 2S, 5R)-(-) - Menthol

glycidic esters, chosen for present study, are shown in table II. They are derived from cyclopentanone, cyclohexanone and cycloheptanone and their synthesis was carried out in an analogous manner as described in the literature[54] with the ketones and menthyl ester of chloroacetic acid.

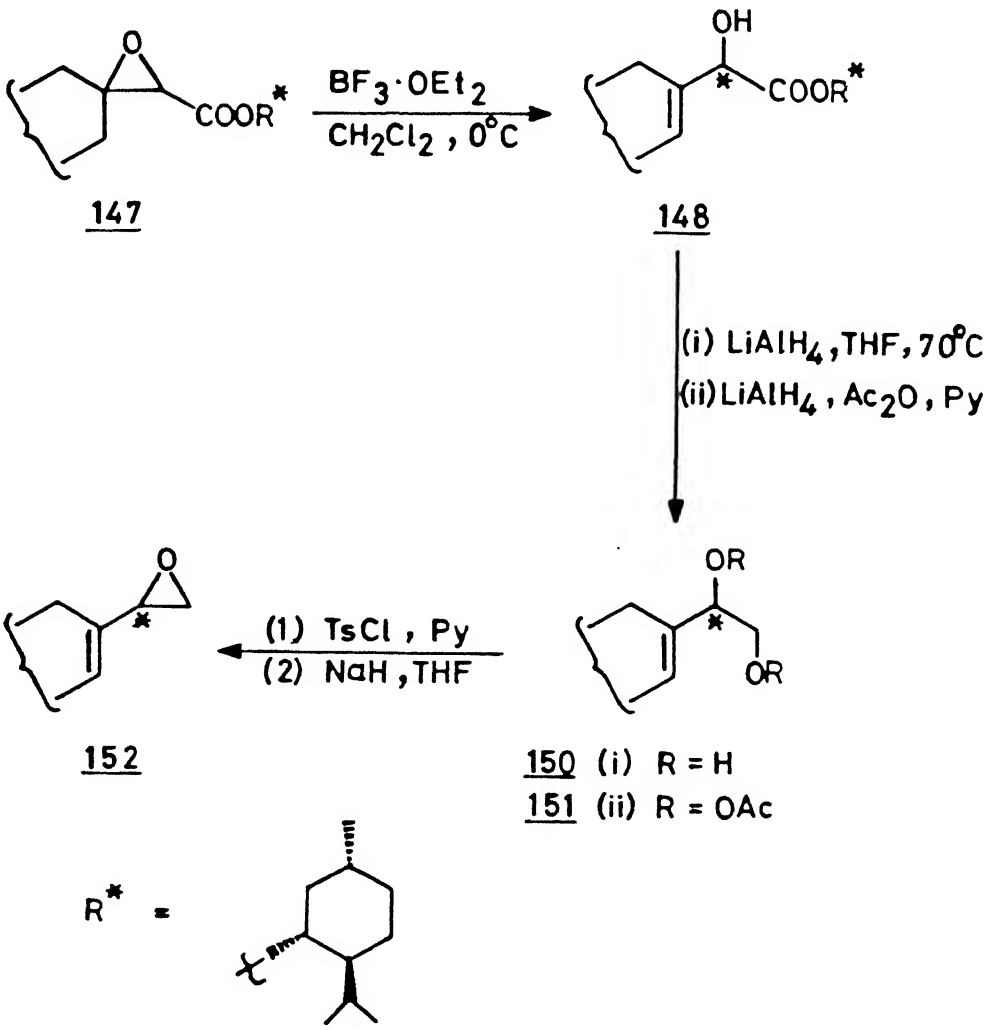


Figure 26

The glycidic ester from cyclohexanone showed two singlets, corresponding to the methine proton on the epoxide ring, one at δ 3.07 and the other one at δ 3.9 in a 3:1 ratio. These singlets could be attributed to the two diastereomers **147b-(I)** and **147b-(II)** (Fig. 27). Isomerisation of this glycidic ester with $BF_3.OEt_2$[53] followed by acetylation gave an acetate **149b** whose ^1H NMR also indicated it to be a mixture of two diastereomers in a ratio of 3:1. The hydroxy ester **148b** upon further reduction with $LiAlH_4$ gave the diol **150b** in 85% yield. This diol was characterised as the corresponding diacetate **151b** whose spectral and analytical details are given in the experimental section. The diol **150b** was converted into the vinyl epoxide by following the procedure as described in section I.9. The vinyl epoxide so obtained showed an optical rotation of $[\alpha]_D^{25}$ = (-) 4.64 (Cl, $CHCl_3$).

Reduction of vinyl epoxide **152b** with $LiAlH_4$ gave the alcohol **153** in 70% yield. The rotation value of this compound was found to be $[\alpha]_D^{25}$ = (-) 6.88 (C1, $CHCl_3$). The structure of this compound was further confirmed by the ^1H NMR spectrum of the corresponding acetate **154**. The methine proton appeared as a quartet at δ 4.96 with a J value of 7 Hz and the methyl group appeared as a doublet at 1.33 with J = 7 Hz. The olefinic proton appeared as a broad singlet at δ 5.6. The alcohol **153** is known in the literature[63] whose absolute configuration is designated as S with specific rotation value of $[\alpha]_D^{25}$ = (-) 9.8 (C 4.25, $CHCl_3$). Since the alcohol **153** obtained in the present study also has a negative sign of rotation its absolute

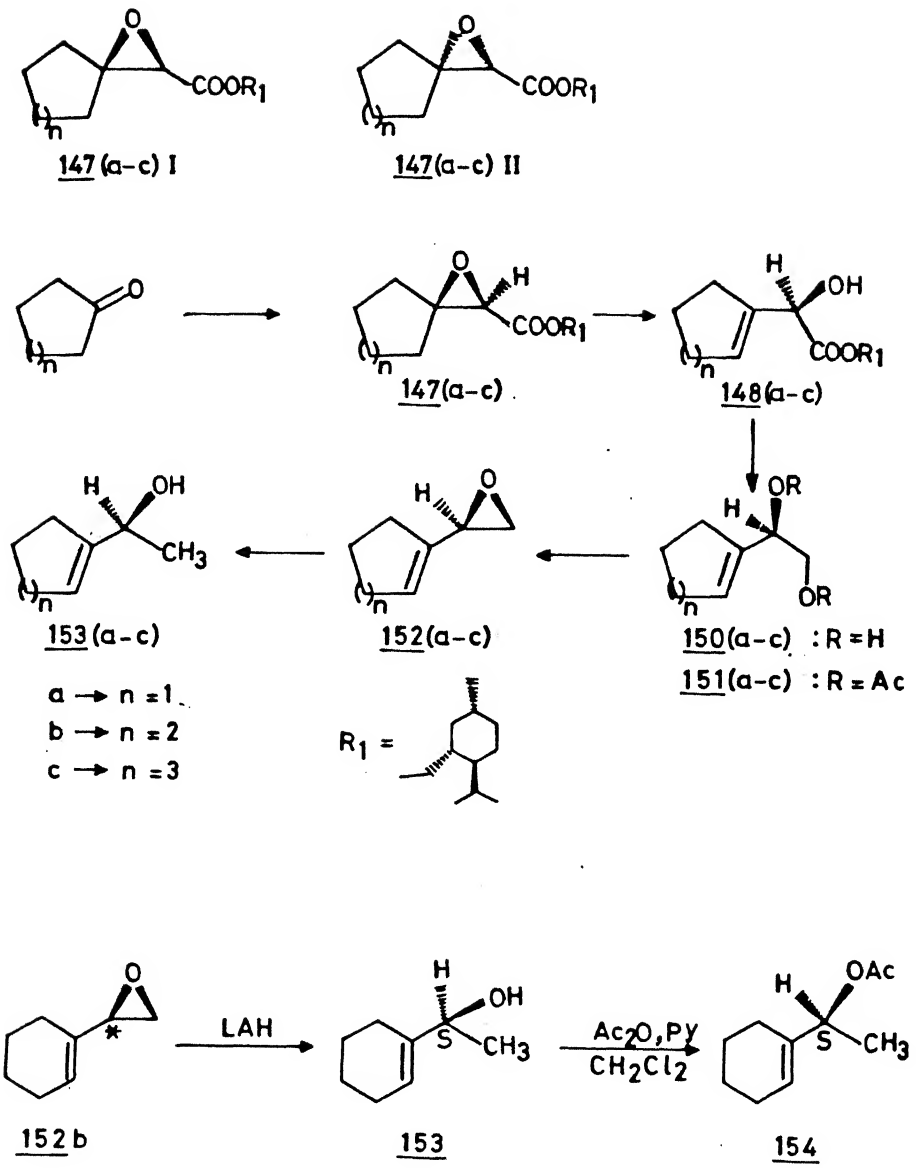

147 (a-c) I
147(a-c) II
147(a-c)
148(a-c)
150(a-c) : R = H
151(a-c) : R = Ac
152(a-c)
153(a-c)
a → n = 1
b → n = 2
c → n = 3
R1 =
152 b
LAH
153
Ac2O, Py
CH2Cl2
154

Figure 27

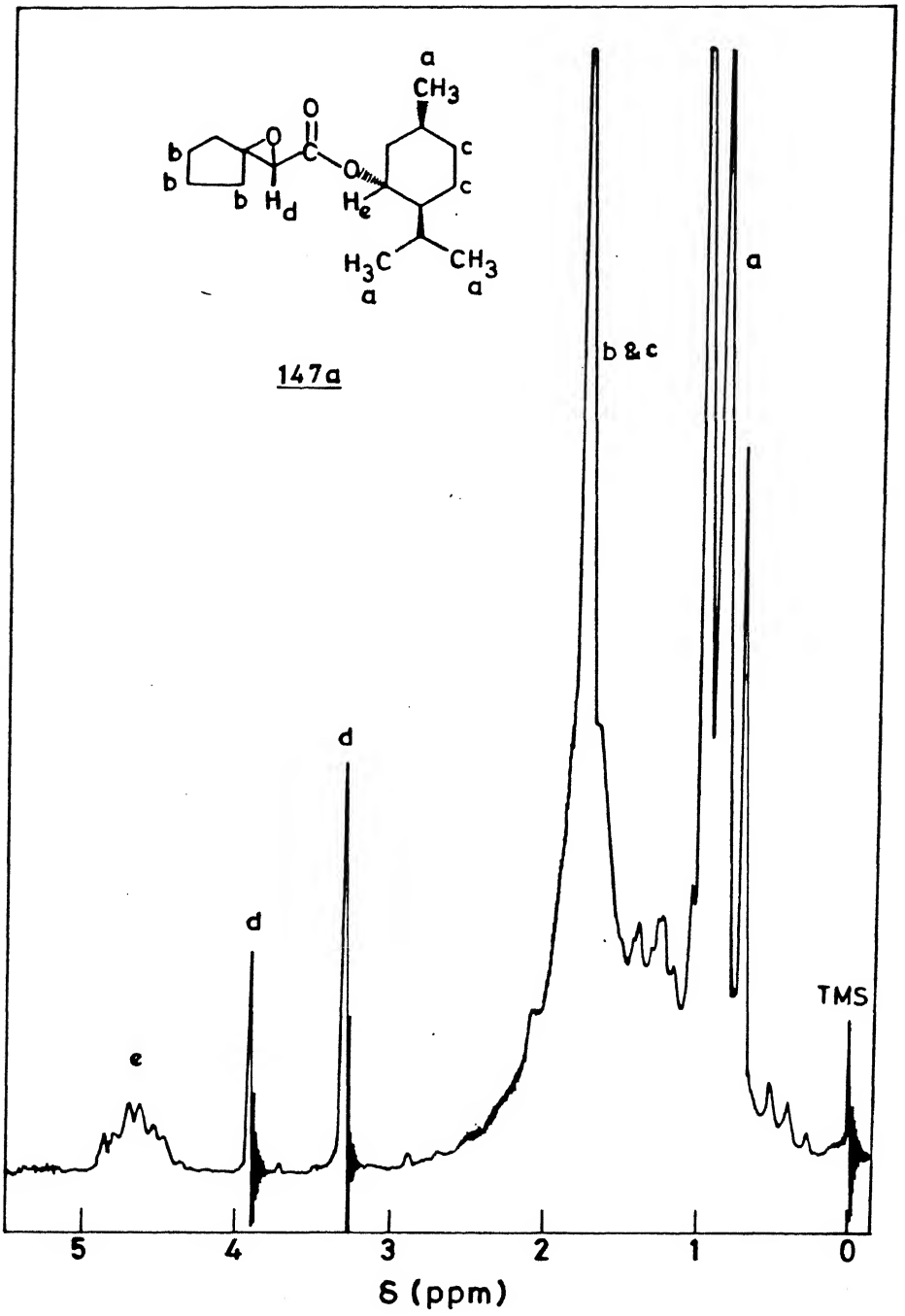


Figure I.4: ^{1}H NMR spectrum (60 MHz) of **147a**

configuration is assigned 'S'. Therefore the major diastereomer of the hydroxy ester as well as the glycidic ester can be written as having the configuration shown in **147b-(I)**.

Likewise, the glycidic ester derived from cyclopentanone which was obtained in 60% yield also showed in its ^1H NMR spectrum, the presence of two diastereomers in a ratio of 3:1. This was concluded on the basis of appearance of two singlets at δ 3.3 and δ 3.9 in a ratio of 3:1 corresponding to the methine proton on the oxirane ring. However these diastereomers **147-I** and **147a-II** were not separable by chromatography. Isomerisation of this glycidic ester **147a** with $BF_3.OEt_2$[53] gave the corresponding α- hydroxy- β, γ - unsaturated ester **148a** whose ^1H NMR spectrum (60 MHz) did not show any separation of the peaks corresponding to the two diastereomers. The vinylic proton appeared as a broad singlet at 5.67 and the methine proton adjacent to the oxygen atom also appeared as a broad multiplet at δ 4.33 - 5.0. On the other hand the corresponding acetate **149a** showed the presence of two diastereomers as was evident from the appearance of two singlets for - $OCOCH_3$ which confirmed that the ratio of the two diastereomers was 3:1. Reduction of the hydroxy ester **148a** with $LiAlH_4$ produced the corresponding diol **150a** in 77% yield. This diol was characterised as the corresponding diacetate whose spectral and analytical details are mentioned in the experimental section (I.14). The specific rotation value of this diacetate was found to be $[\alpha]_D^{25}$ = (-) 39.04 (C1, $CHCl_3$). The diol **150a** was transformed into vinyl epoxide **152a** in two steps as described in the section (I.15).

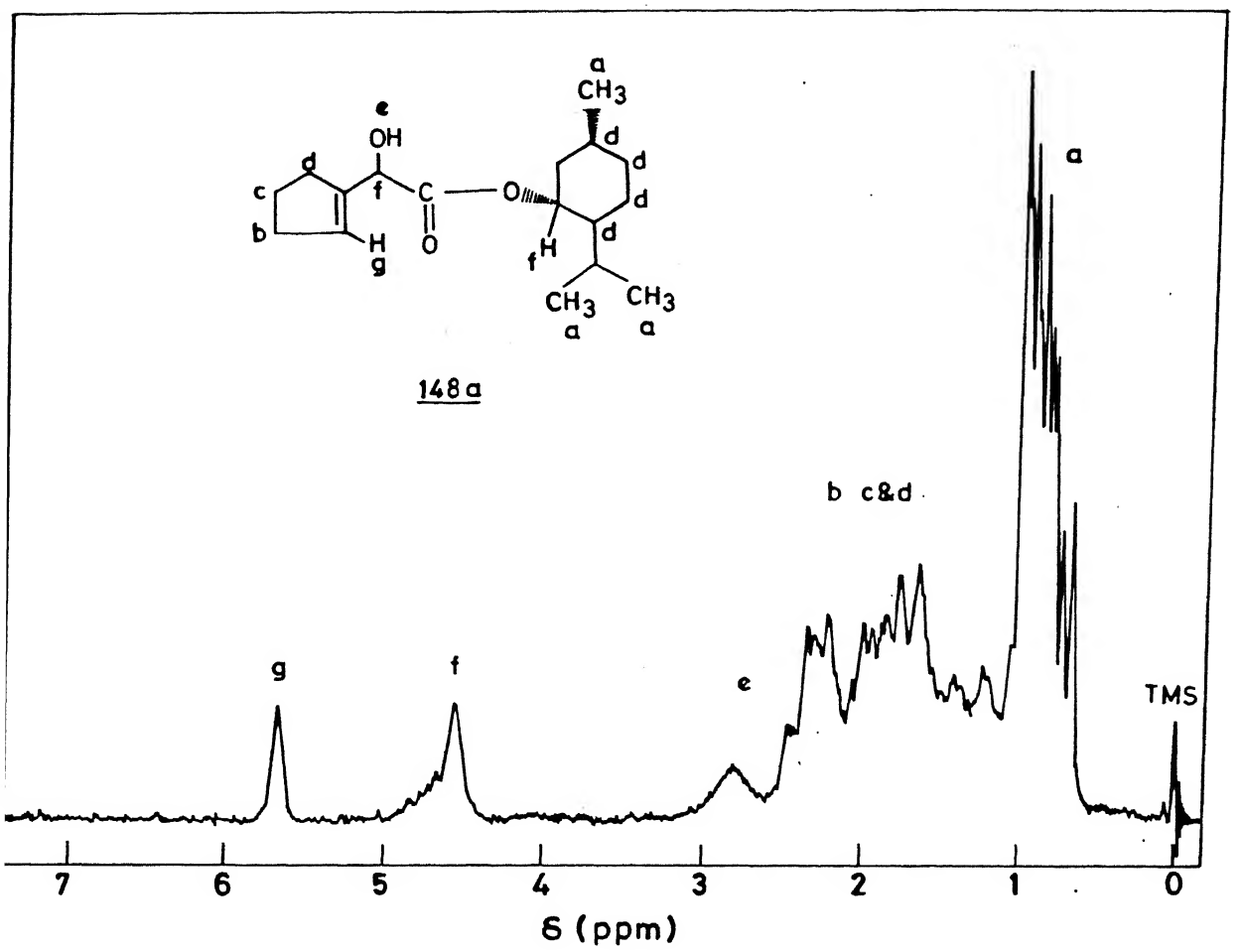


Figure I.5: ^{1}H NMR spectrum (60 MHz) of **148a**

This vinyl epoxide, obtained in 59% yield, had $[\alpha]_D^{25}$ = (-) 1.23 (Cl, $CHCl_3$). Its ^1H NMR spectrum, however, did not show any separation of the two enantiomers in the presence of a shift reagent. On the other hand, since the glycidic ester was found to be a mixture of two diastereomers in a ratio of 3:1 and since the asymmetric centre was neither destroyed nor changed, it is believed that the vinyl epoxide was also a mixture of two enantiomers in a ratio of 3:1. It is therefore concluded that this vinyl epoxide is having 50% enantiomeric excess. For obtaining a complete proof for this e/e more work is obviously required.

The absolute configuration of the hydroxy ester **148a**, the glycidic ester **147a** as well as that of vinyl epoxide **152a** can be written on the basis of extrapolating the arguments used for cyclohexane system. Since the rotation for vinyl epoxide **152a** was also negative its configuration is as shown in (Fig. 27).

In the case of cycloheptane system the glycidic ester showed only one singlet at δ 3.15 for the methine proton present on the oxirane ring. Unlike in cyclopentane and cyclohexane systems the two diastereomers, if at all present in cycloheptane case, did not show the separation of the methines due to them in its ^1H NMR spectrum. On the other hand the acetate **149c** derived from the isomerised hydroxy ester showed the presence of two diastereomers in a ratio of about 3:1. This was concluded on the basis of the presence of two signlets due to the - $OCOCH_3$ protons present at δ 2.0 and δ 2.07. The diol **150c** was characterised as its diacetate, the spectral details of which are given in the experimental section. Conversion of the diol

into the vinyl epoxide **152c** was carried out via its tosylate. The vinyl epoxide obtained showed specific rotation value of $[\alpha]_D^{25}$ = (-) 5.48 (Cl, $CHCl_3$). The absolute configuration of the major isomer of vinyl epoxide **152c** as well as its precursors, till the glycidic esters could therefore be written as shown in the structures **147c-153c** (Fig. 27) on the basis of the same arguments as were used for cyclopentane system.

Since the optical purity of the vinyl epoxides and their precursors was only of the order of 50%, it was considered worth studying an alternate way of inducing asymmetry and thereby hoping that, the e.e would be of higher value. Towards this goal we considered the possibility of using enzymatic resolution technique.

Use of enzymes in organic synthesis has gained importance during the last few years. Ester hydrolysis with the aid of enzymes viz. hydrolases has long been employed in organic synthesis particularly for the kinetic resolution of chiral carboxylic acids and alcohols. Porcine liver esterases (PLE) and various lipases are most frequently utilised because they are inexpensive and are tolerant to a wide range of substrates.

Sih[64,65] et al were the first to realize the potential of kinetic resolution of meso diesters. They hydrolysed dimethyl cis-2,4-dimethyl glutarate **155** by PLE and Gliocladium Roseum which produced the half esters **156** and **157** in 64% and 91% e.e. respectively. Gais[66] and Schneider[67] have obtained tetrahydrophthalate half ester **159** on 100 mole scale using PLE. This compound was produced in 98% chemical yield and with at least 98% ee. This half ester subsequently has been transposed

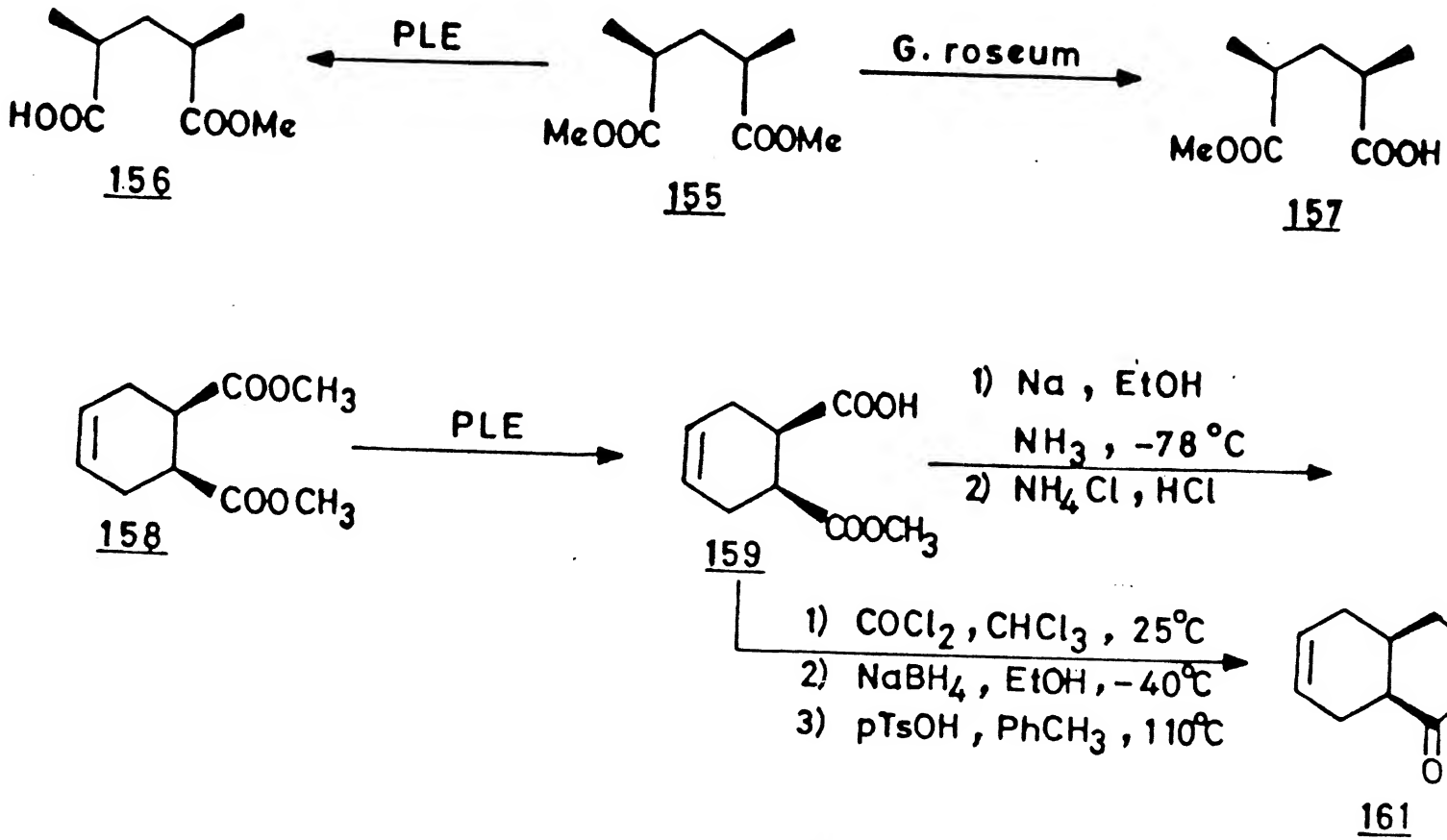

PLE
G. roseum
HOOC
COOMe
156
MeOOC
COOMe
155
MeOOC
COOH
157
COOCH3
COOCH3
158
PLE
COOH
COOCH3
159
1) Na , EtOH
NH3 , -78 °C
2) NH4Cl , HCl
160
1) COCl2 , CHCl3 , 25°C
2) NaBH4 , EtOH , -40°C
3) pTsOH , PhCH3 , 110°C
161

Figure 28

into bicyclic lactones **160** and **161** (Fig. 28) of opposite enantiomeric series through chemoselective reaction.

A variety of cyclic meso diesters have been converted into optically active half esters in an analogous manner by Tamm[68], Ohno[69] and Jones[70]. In addition to the meso diesters the asymmetric hydrolysis of meso diacetates into the corresponding hydroxy acetates in optically pure form has also been reported in the literature.

For example the meso diacetate[65] **162** (Fig. 29) has been transformed into the enantiomeric hydroxy acetates **163** and **164** using two different enzymes viz. PLE and acetylcholine esterase (Fig. 29). Thus, depending on the type of enzyme employed both enantiomeric forms of valuable importance can be prepared.

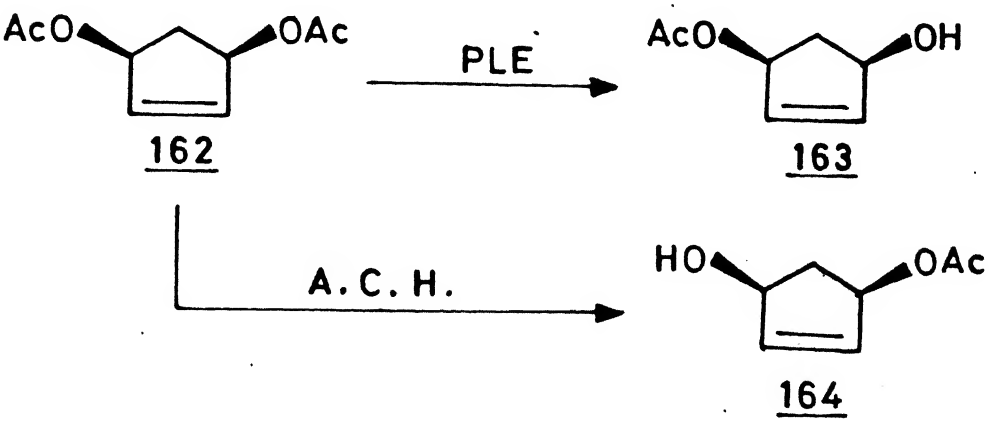
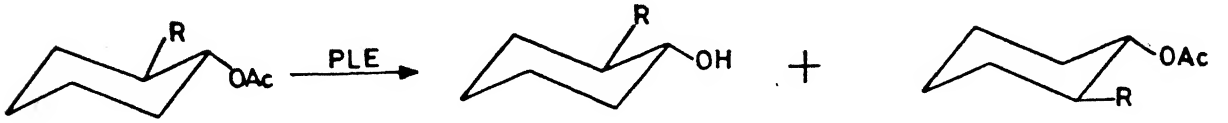


Figure 29

It has recently been demonstrated[71-73] that results comparable to those from PLE can be obtained with an easily prepared crude extract from fresh pig liver, a factor that is likely to decrease the cost of frequent application of the method and will increase its popularity. Whitesell was able to separate pure enantiomers from the racemic mixture of the esters **165a** and **165b** with this crude extract. In the case of **165a** 6 days of reaction yielded an approximately 1:1 mixture of (-) **166a** and (+) **165a** which was separated by chromatography. Basic hydrolysis of (+) **165a** gave (+) **166a**. Thus, both the enantiomers were obtained in high optical purity. Likewise enantiomers from **165b** were also separated (Fig. 30).



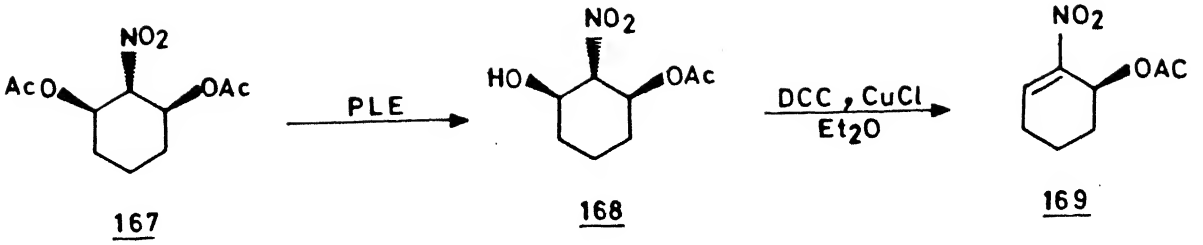
(±) 165a R = Ph
(±) 165b R = Me_2CPh

(-) 166a
(-) 166b

(+) 165a
(+) 165b

Figure 30

Similarly Seebach[72] has used hydrolysis of the diacetates of 2-nitro-1, 3-diols with crude extracts of fresh pig liver to obtain in optically active form of such 2-nitro-allyl esters as **169** (Fig. 31). This compound is of special interest because it can act as two fold Michael acceptors. The hydrolysed acetates were obtained in (90-97)% e.e.



167 168 169

Figure 31

The use of crude pig liver esterase in the form of powder known as pig liver acetone powder (PLAP) has been demonstrated by a number of chemists[69,72a,73,74] to prepare a variety of optically active compounds. A few representative examples of such reactions are shown in the fig. 32.

In view of the above mentioned developments using PLAP to resolve the racemic acetates as well as esters we were prompted to use it in resolving (±) α-hydroxy- β,γ-unsaturated ester. Initial attempt to hydrolyse hydroxy ester **119b** (cf. Table III) with fresh PLAP did not result in any appreciable yield. Even after several days of the reaction more than 95% of the starting hydroxy ester was recovered. Although this recovered hydroxy ester did show specific rotation to be $[\alpha]^{25}_{D}$ = (+) 5.183 (Cl, $CHCl_3$), the corresponding hydroxy acid could not be isolated. Since the hydrolysis was not appreciable we attempted the hydrolysis of the corresponding acetate i.e. (±) **178**. It was expected that such a compound possessing an acetate and an ester group might undergo hydrolysis at least on one of these two centres. The acetoxy ester was prepared by acetylation of (±) **119b** in 82% yield using pyridine, DMAP, AC_2O. Treatment of this

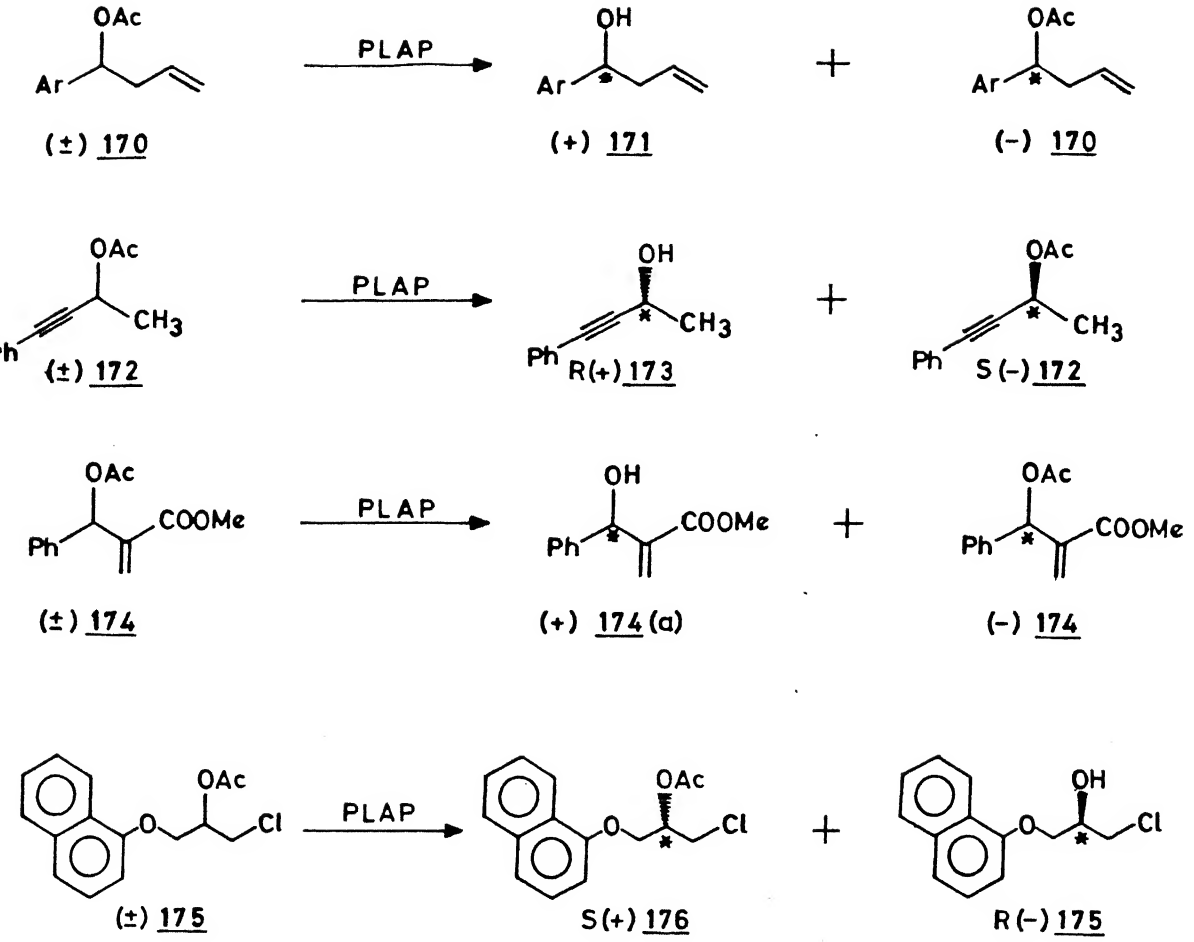

OAc
Ar
PLAP
OH
Ar
+
OAc
Ar
(±) 170
(+) 171
(-) 170
OAc
CH3
PLAP
OH
CH3
+
OAc
CH3
Ph
Ph
Ph
(±) 172
R(+) 173
S(-) 172
OAc
Ph
COOMe
PLAP
OH
Ph
COOMe
+
OAc
Ph
COOMe
(±) 174
(+) 174(a)
(-) 174
OAc
O
Cl
PLAP
OAc
O
Cl
+
OH
O
Cl
(±) 175
S(+) 176
R(-) 175

Figure 32

racemic acetoxy ester **178** with PLAP under standard conditions as described in the literature[64] was carried out. The hydrolysis was completed after 72 hrs. The hydrolysed alcohol i.e. the hydroxy ester (+) **119b** was obtained in 81% yield and with specific rotation value: $[\alpha]^{25}_{D}$ = (+) 35. 563 (Cl, $CHCl_3$). The enantiomeric excess of this alcohol was found to be 90% on the basis of the ^{1}H NMR analysis of its Mosher's ester (derived from R- (+)- α -methoxy - α - (trifluoromethyl) phenyl acetic acid). This analysis was based upon the integration of the methoxy peaks. The Mosher's ester of the corresponding racemic alcohol showed two singlets for the two enantiomers at δ 3.52 and δ 3.62 of equal intensity. On the other hand the Mosher's ester of resolved alcohol showed two singlets for the methoxy protons in a ratio of 95:5 at δ 3.54 and δ 3.64. The enantiomeric excess of the resolved acetate (-) **178** based on ^{1}H NMR analysis using chiral shift reagent i.e. (+) $Eu(hfc)_3$: [(Tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato] europium (III)] was found to be 54%. The value of the e.e. was determined in this case on the basis of the integration value of acetate peaks.

The racemic hydroxy ester **119a** was converted into the corresponding acetate **177** and the same was hydrolysed using PLAP in an analogous manner as described above. The reaction after 64 hrs of stirring was worked up to afford the optically active hydroxy ester (+) **119a** whose specific rotation was found as $[\alpha]^{25}_{D}$ = (+) 29.016 (Cl, $CHCl_3$).

Determination of enantiomeric excess of (+) **119a** alcohol was again carried out on the basis of ^{1}H NMR spectral analysis of the

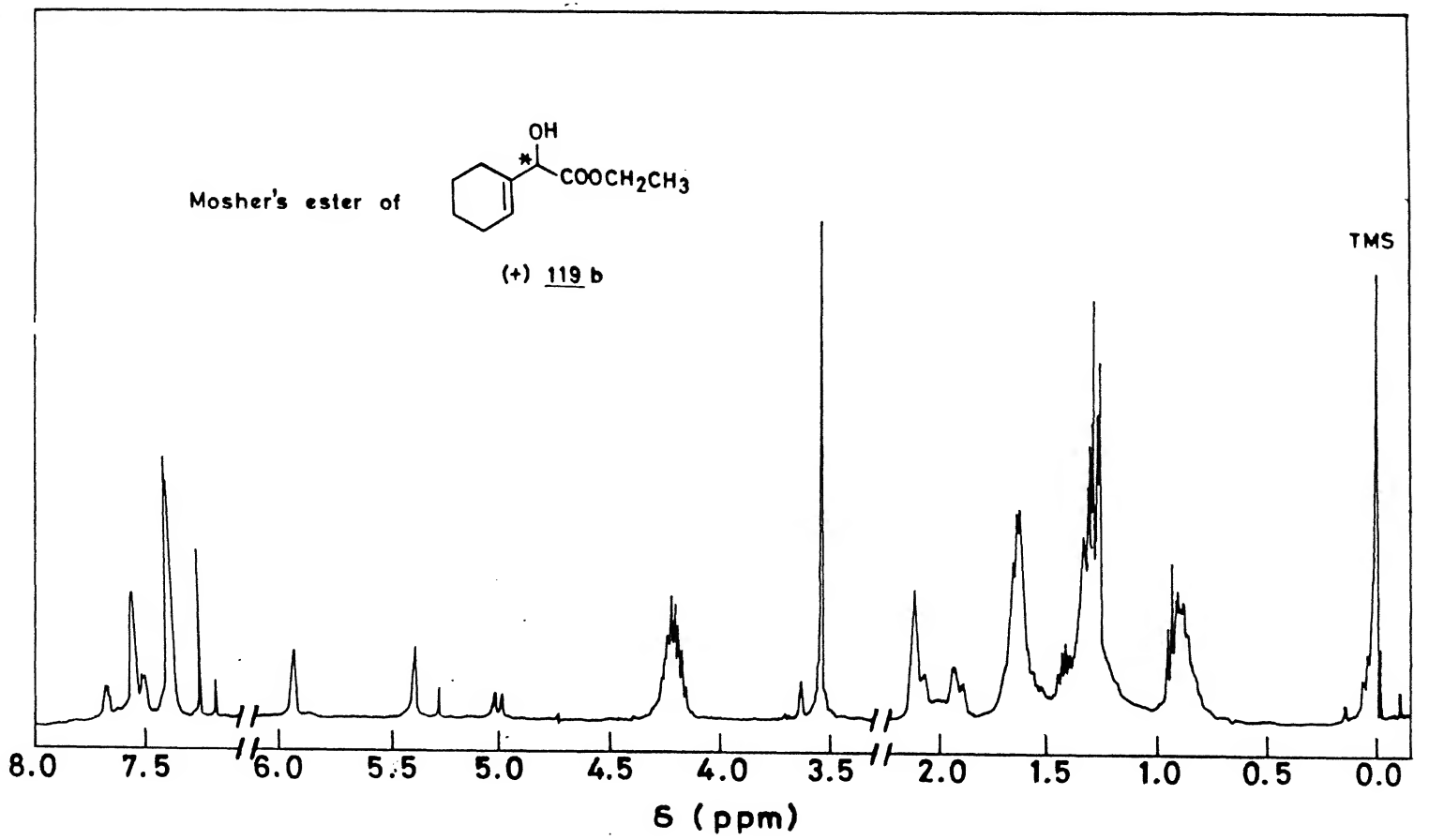


Figure I.6: ^{1}H NMR spectrum(400MHz) of Mosher's ester of (+)**119b**

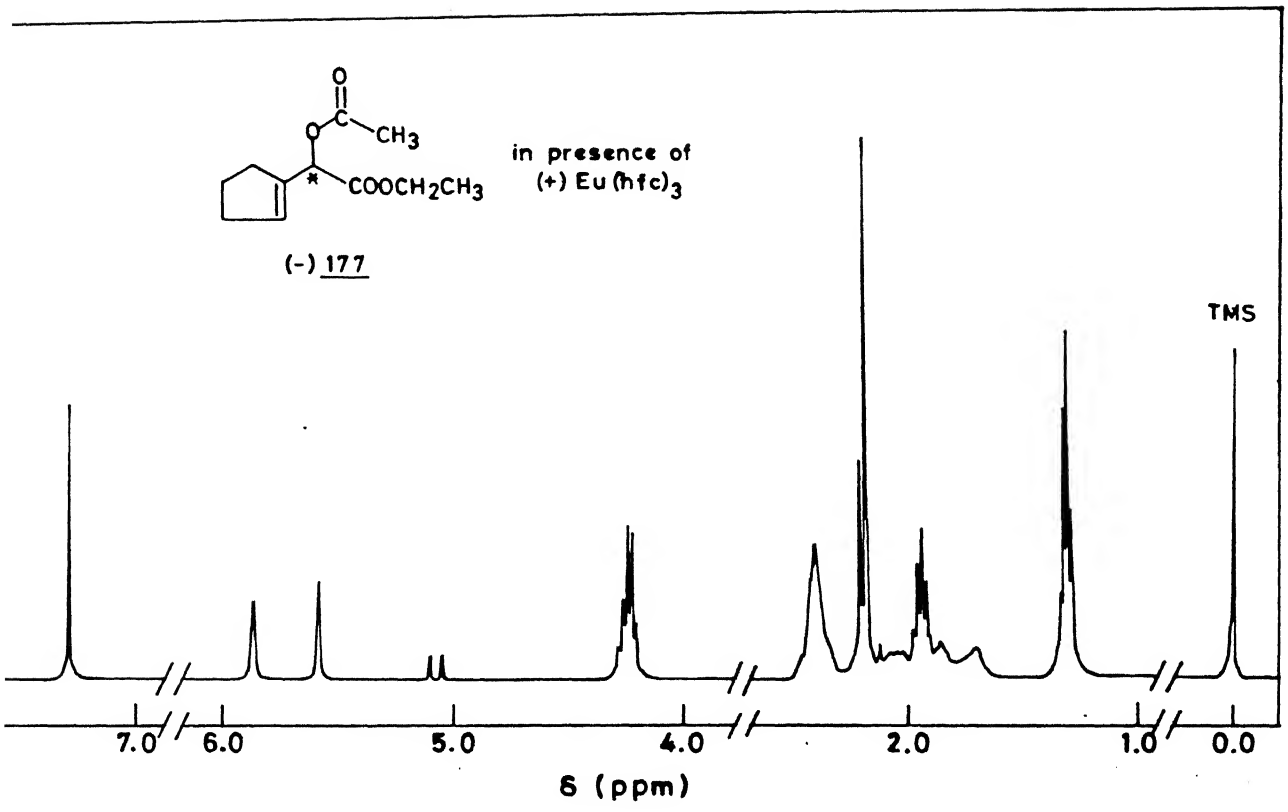


Figure I.7: ^{1}H NMR spectrum(400MHz) of (-) **177**

corresponding Mosher's ester. The methoxy protons appeared as two singlets at δ 3.56 and at δ 3.66 in a ratio of 91:9 indicating thereby that the e.e. of this hydroxy ester is 82%. The corresponding unhydrolysed acetate (-) **177** showed optical rotation to be $[\alpha]^{25}_{D}$ = (-) 28.475 (Cl, $CHCl_3$). ^1H NMR spectrum 400 MHz) of this acetate in the presence of chiral shift reagent (+) $Eu(hfc)_3$ showed two peaks of the acetates as δ 2.17 and δ 2.20 in the ratio of 72:28 indicating e.e. to be 44%.

In order to study the generality of these reactions a few more examples were studied. These included α-hydroxy- β, γ -unsaturated esters derived from cycloheptanone, 4 -phenyl cyclohexanone, acetophenone, acetone and 3-pentanone. With cycloheptane system the hydroxy ester (+) **119c** showed the specific rotation to be $[\alpha]^{25}_{D}$ = (+) 108.14 (Cl, $CHCl_3$) which was obtained in 35% chemical yield. The enantiomeric excess (e.e.) on the basis of its Mosher's ester was found to be 80%. The enantiomeric excess (e.e) of the recovered acetate, whose specific rotation was $[\alpha]^{25}_{D}$= (-) 82.56 (Cl, $CHCl_3$), was estimated to be 34% from its ^1H NMR spectral analysis in the presence of (+) $Eu(hfc)_3$.

The α-hydroxy- β, γ -unsaturated ester **119e** derived from 4-phenyl cyclohexanone, as described in the beginning, was acetylated using pyridine, acetic anhydride, DMAP system. Hydrolysis of this acetoxy ester with PLAP gave the corresponding resolved hydroxy ester in only 29% yield. However, unlike the previous cases, as described above, the specific rotation value

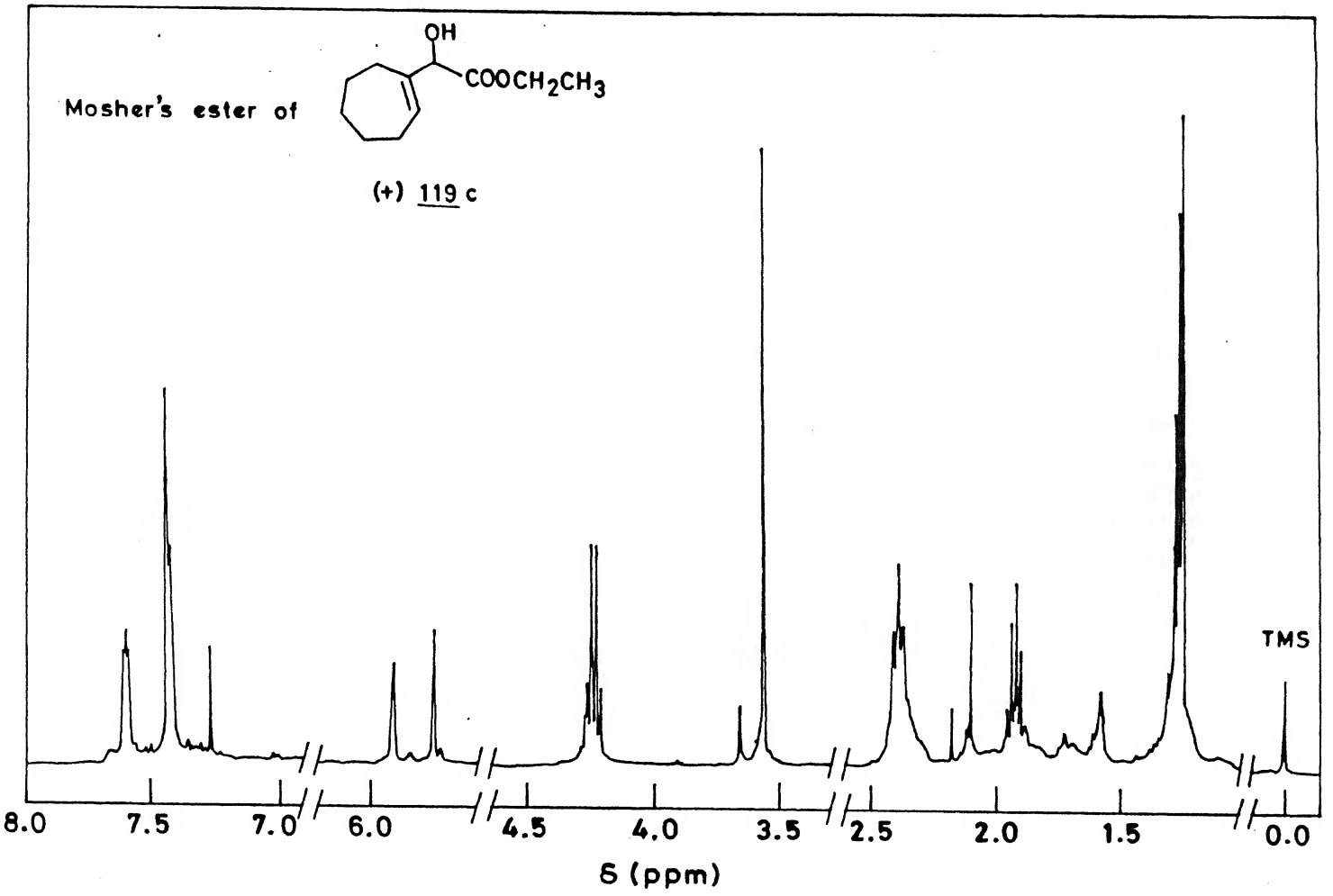
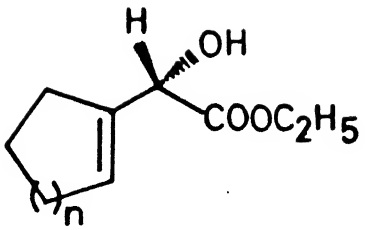
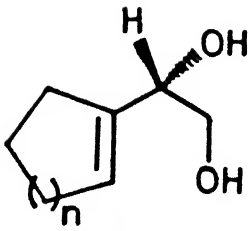


Figure I.8: ^{1}H NMR spectrum (400 MHz) of Mosher's ester of (+) **119c**

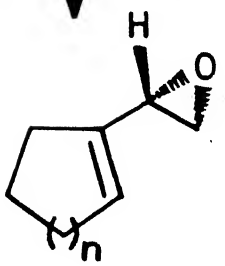


LAH, THF
60°C

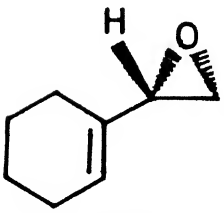


n = 1 ; (+) 119 a
n = 2 ; (+) 119 b
n = 3 ; (+) 119 c

(i) TsCl, Py, ether, -10°C
(ii) NaH, THF, 10°C

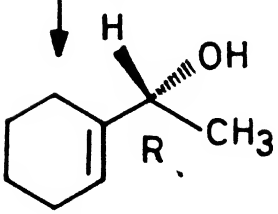


n = 1 ; (+) 152 a
n = 2 ; (+) 152 b
n = 3 ; (+) 152 c



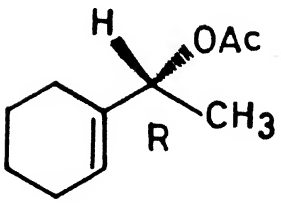
(+) 152 b

LAH, THF, 30°C



(+) 153

Ac_2O, Py
CH_2Cl_2, RT



(+) 154

Figure 33

of this alcohol was negative: $[\alpha]^{25}_{D}$ = (-) 7.8554 (Cl, $CHCl_3$). The enantiomeric excess of this alcohol, determined through its Mosher's ester, was found to be 69%. The specific rotation of the recovered acetate was found to be $[\alpha]^{25}_{D}$ = (+) 9.7419 (Cl, $CHCl_3$). Its ^1H NMR spectral analysis (400 MHz) in the presence of (+) $Eu(hfc)_3$ showed its enantiomeric excess to be 53%. The sign of the rotation values of the alcohol and the acetate were opposite from the ones observed in the previous cases.

The absolute configuration of the hydroxy ester or the glycidic ester was assigned in the case of cyclohexanone system by comparison with the literature[63] value of **153**. By a logical extension the configurations of cyclopentane system and cycloheptane system were assigned since the sign of the rotation values were the same as that of cyclohexane system.

The hydroxy ester (+) **119b** obtained from the PLAP hydrolysis of the corresponding acetate (±) **178** was reduced with $LiAlH_4$ to the corresponding diol which was converted into the corresponding vinyl epoxide via its tosylate as described in the synthesis of achiral vinyl epoxide **122b**. The spectroscopic details of this vinyl epoxide (+) **152b** were identical, as expected, with that obtained for the vinyl epoxide (-) **152b** except that its sign of rotation was opposite. The corresponding reduced product (+) **153** as expected, also showed positive rotation value i.e. $[\alpha]^{25}_{D}$ = (+) 12.15 (Cl, $CHCl_3$). The absolute configuration of this alcohol thereby, will be R as shown in (Fig. 33). Thus the two methods viz., one via (-) menthol derivative and the other via PLAP hydrolysis are complimentary to each other. The absolute configurations of hydroxy esters derived from cycloheptane and

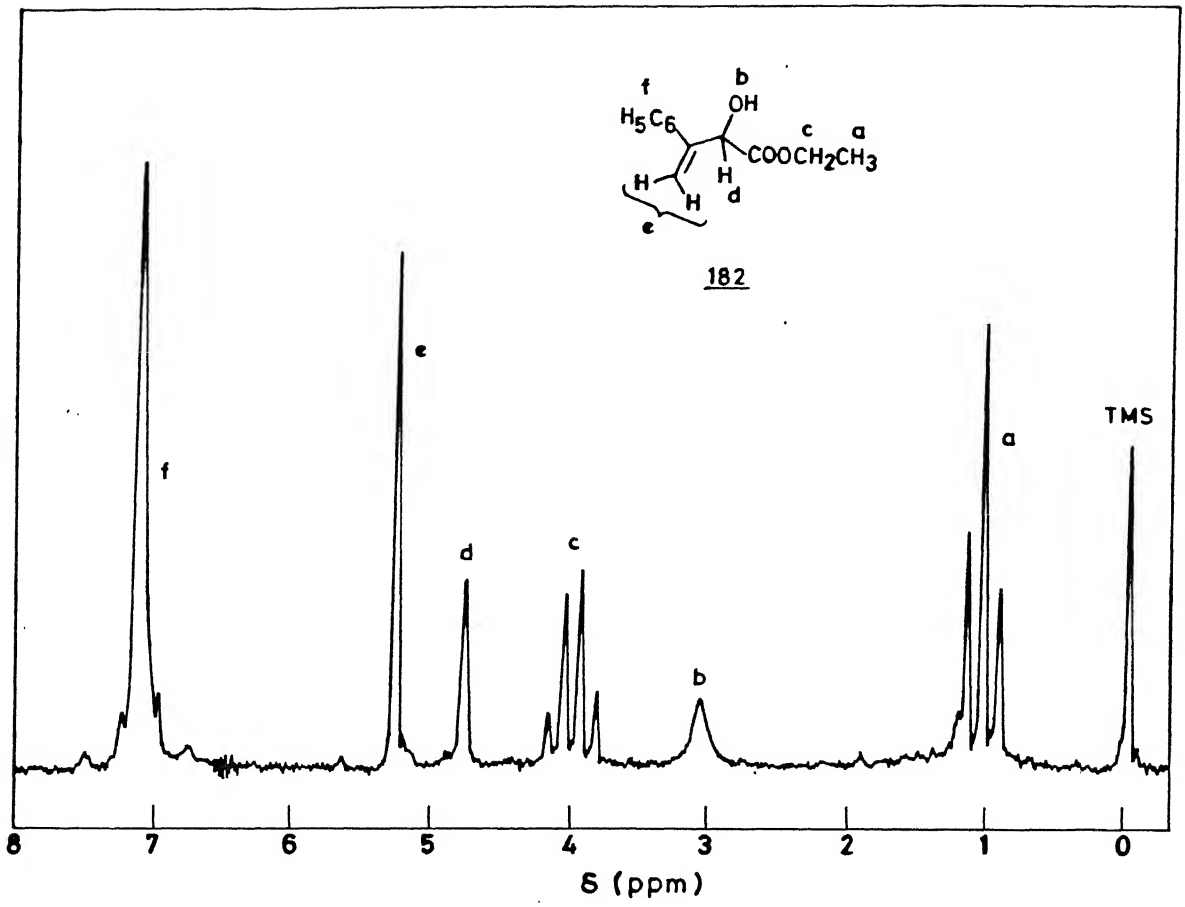
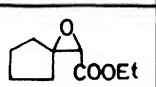
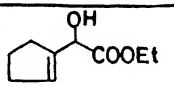
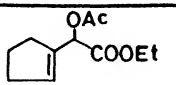
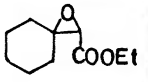
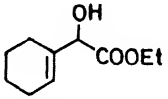
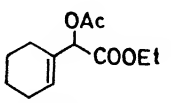
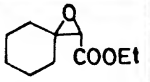
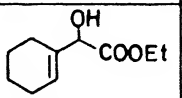
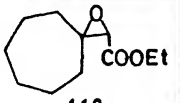
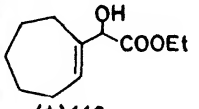
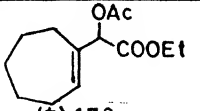
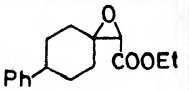
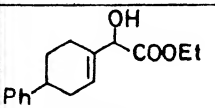
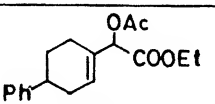
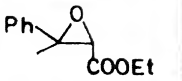
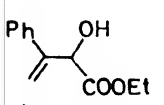
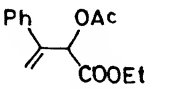
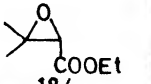
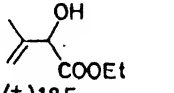
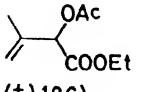
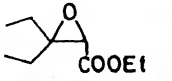
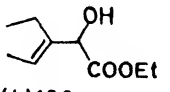
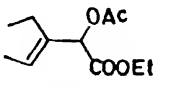


Figure I.9: ^{1}H NMR spectrum (60 MHz) of **182**

Entry	Glycidie Ester	(±) Hydroxy Ester	Acetoxy Ester	Chiral Alcohol			Chiral Acetate		
				Compound	$[\alpha]_D^{25}$ C1 $CHCl_3$	e e	Compound	$[\alpha]_D^{25}$ C1 $CHCl_3$	e e
1	 118a	 (±)119a	 (±) 177	(+)119 a	(+)29.016	82 %	(-) 177	- 28.475	44 %
2	 118b	 (±)119 b	 (±)178	(+) 119 b	(+)35.563	90 %	(-) 178	- 28.473	54 %
3	 (+)118b	 (±)119 b		(+) 119 a	(+)5.183				
4	 118c	 (±)119c	 (±) 179	(+) 119 c	(+)108.14	80 %	(-) 179	(-) 82.56	34 %
5	 118e	 (±)119e	 (±) 180	(-) 119 d	(-)7.8554	69 %	(+) 180	(+)9.7419	53 %
6	 181	 (±)182	 (±) 183	(+) 182	(+)6.69	65 %	(-) 183	(-) 8.79	20 %
7	 184	 (±)185	 (±) 186)				(-) 186	(-)15.033	40 %
8	 187	 (±)188	 (±) 189				(-) 189	(-)20.890	29 %

55(A)

cyclopentane systems would therefore be as indicated in the structures (+) **119c**, and (+) **119a** respectivey. However, since the sign of the rotation value is negative in 4-phenyl cyclohexane system, the absolute configuration could be opposite to that of ∝-hydroxy esters (+) **119a** , (+) **119b** and (+) **119c**. On the other hand, the substitution of the phenyl group at position 4 could change the sign of rotation while the absolute configuration of the asymmetric centre remaining the same as obtained for compounds (+) **119a**, (+) **119b** and (+) **119c**. Confirmation of this aspect needs to be carried out in an unequivocal manner.

For reactions in acyclic series the first example studied was from acetophenone. Isomerisation of the corresponding glycidic ester was carried out using sulfuric acid[75] rather than $BF_3.OEt_2$. The hydroxy ester (±) **182**, obtained in 48% yield, was then converted into the corresponding acetate ester using standard procedure as mentioned for other acetate esters and characterised spectroscopically (cf. I.19). PLAP hydrolysis of this compound gave the hydroxy ester (+) **182** in 36% yield whose specific rotation value was found to be $[\alpha]^{25}_D$ = (+) 6.69 and its enantiomeric excess derived from its Mosher's ester was found to be 65%. The recovered acetate which had specific rotation $[\alpha]^{25}_D$ = (-) 8.79 was found to be having 20% e.e as revealed by its 400 MHz ^1H NMR spectrum. The $-O-COCH_3$ protons appeared as two singlets in the ratio of 40:60 at 2.44 and 2.46.

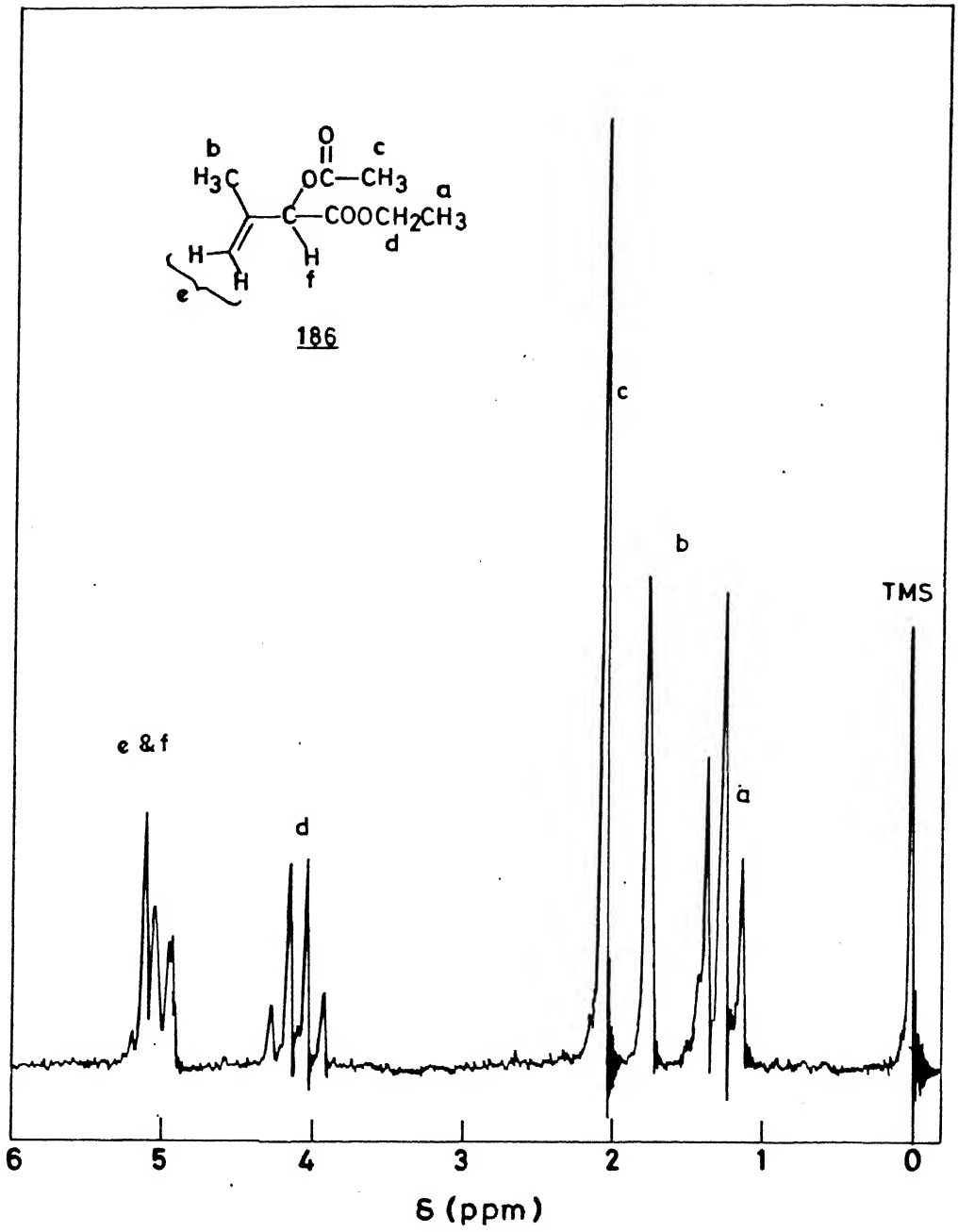


Figure I.10: ^{1}H NMR spectrum(60MHz) of **186**

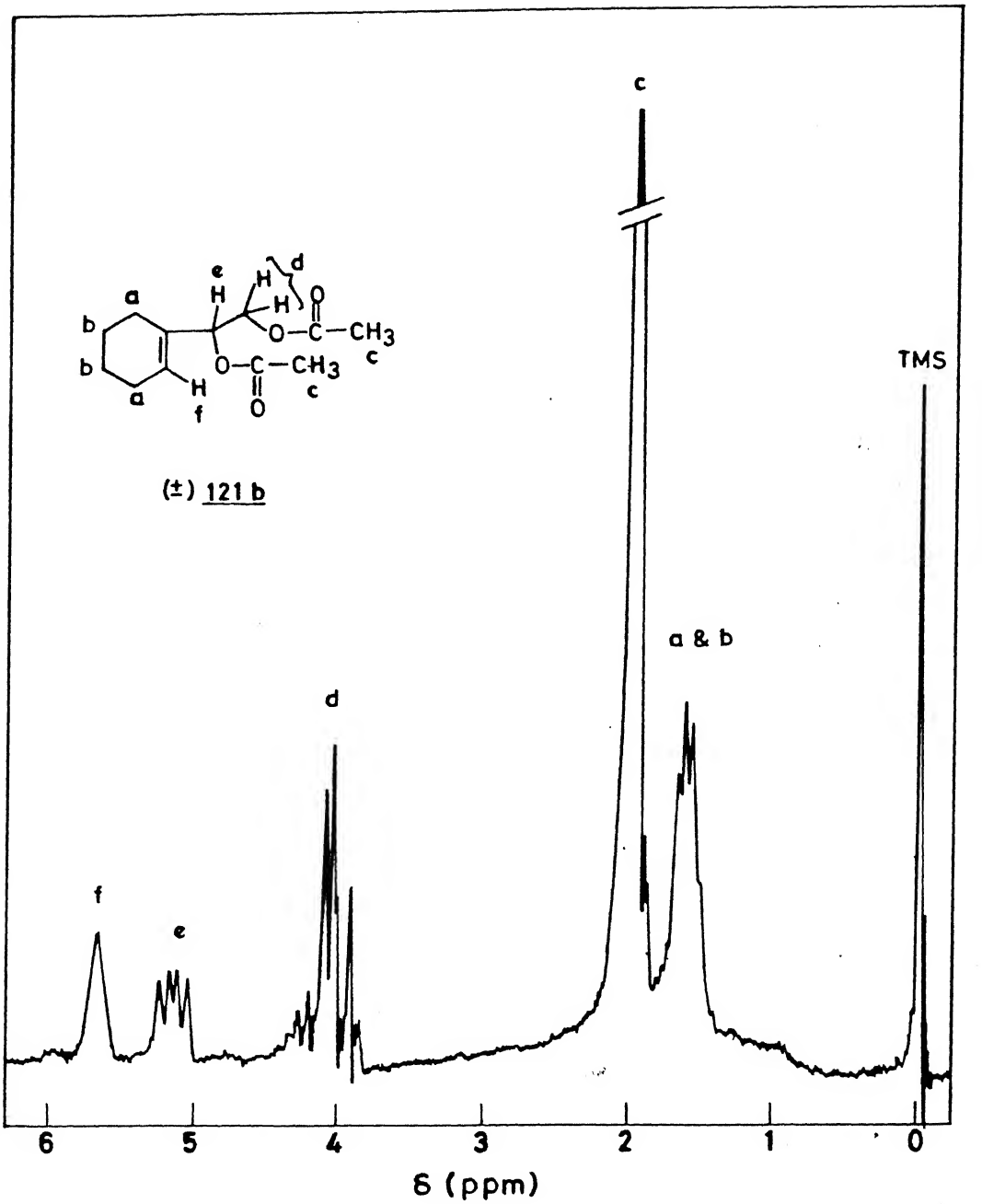


Figure I.11: ^{1}H NMR spectrum (60 MHz) of (±) **121b**

The glycidic ester from acetone was isomerised[75] with sulfuric acid and the corresponding α-hydroxy ester was acetylated. PLAP hydrolysis of this acetate even after 70 hrs did not show any appreciable hydrolysis as revealed by the TLC analysis of the reaction mixture. However, the recovered acetate (-) **186** was found to be optically active with a rotation value of $[\alpha]^{25}_{D}$ = (-) 15.033 (Cl, $CHCl_3$). In the presence of (+) $Eu(hfc)_3$ the 400 MHz ^1H NMR spectrum of this acetate revealed its e.e to be about 40% as the $-O-COCH_3$ protons appeared as two singlets at δ 2.502 and δ 2.506 in the ratio of 70:30. The hydrolysed alcohol, however, could not be isolated from the reaction mixture. Since the recovered acetate was isolated in large amount it is probable that the small amount of the alcohol formed in the reaction may have got lost during the workup owing to its low molecular weight and higher polarity.

The α-hydroxy-β,γ-unsaturated ester derived from 3-pentanone was synthesized in an analogous manner as reported in the literature[75]. This hydroxy ester was characterised as acetate **189** and was found to be a mixture of E and Z isomers in approximately 2:1 ratio. In its ^1H NMR spectrum the vinylic methyl group appeared as two doublets at δ 1.63 and δ 1.7 in 2:1 ratio. The methine proton (>CHOAc) appeared as two singlets at δ 5.03 and the other at δ 5.06 accounting for 1 proton and representing the two geometrical isomers. Although it was a mixture of two geometrical isomers the PLAP hydrolysis was still carried out and no further studies were done to ascertain the ratio of cis and trans isomers.

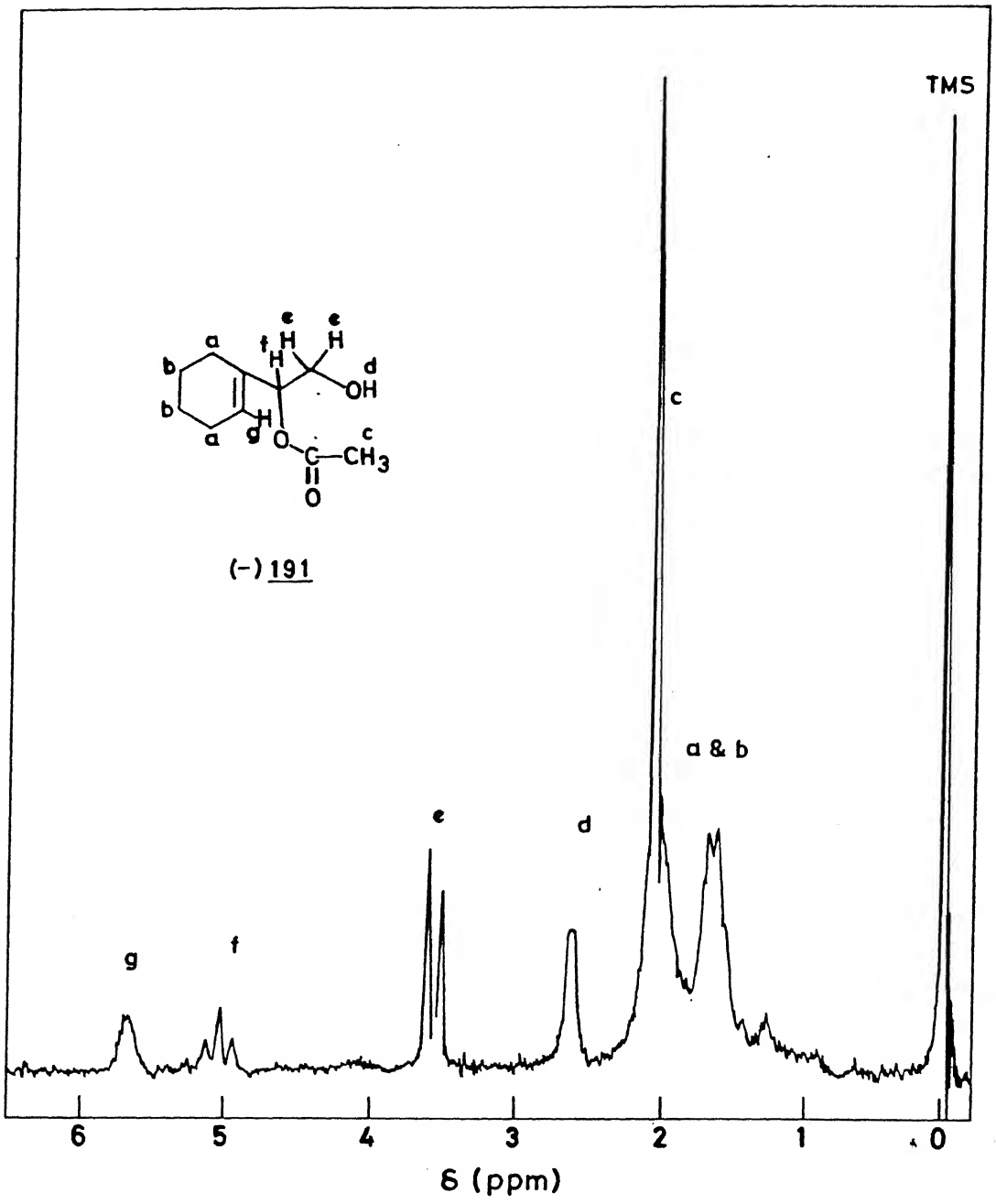


Figure I.12: ^{1}H NMR spectrum (60 MHz) of (-) **191**

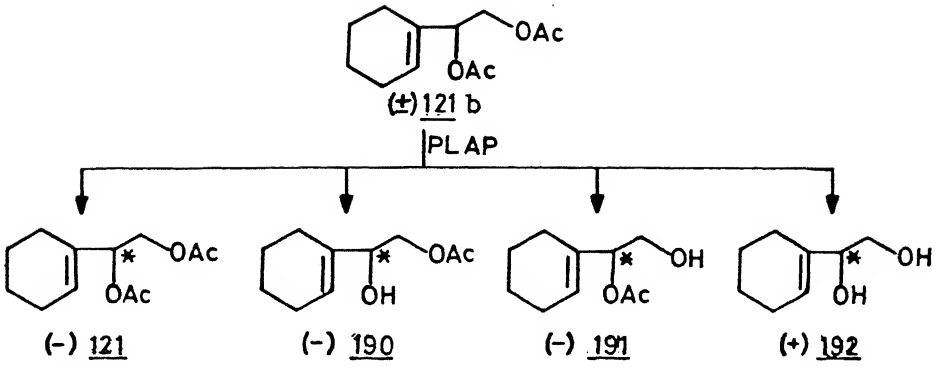


Figure 34

in this case no attempt was made to study the hydrolysis of diacetates from other examples. Spectroscopic details of compounds **190**, **191** and **192** are presented in the experimental part.

This study using PLAP hydrolysis therefore leads to a number of optically pure hydroxy esters and vinyl epoxide (+) **152b** and the alcohol (+) **153** in fairly good optical purity. These compounds show opposite configurations in comparison to those which are obtained using (-) menthol. These intermediates are expected to be useful in organic synthesis.

I.4 Experimental details

All the reactions were performed in oven dry glass apparatus. Reaction mixtures were stirred magnetically. Commercial grade solvents were distilled before use. Dichloromethane used for the reactions was distilled from phosphorous pentoxide (P_2O_5). Xylene and Benzene were dried over $CaCl_2$ and stored over sodium wires. THF was dried over potassium hydroxide (KOH) and stored over sodium wires. Pyridine was distilled and stored over KOH. Acetic anhydride was freshly distilled and boron trifluoride etherate was also freshly distilled over calcium hydride (CaH_2) before use. t-Butanol was dried using anhydrous K_2CO_3. Acetone was dried using $KMnO_4$, anhydrous K_2CO_3 and finally used after distillation. Acetophenone and 3-pentanone were distilled prior to use.

Thin layer chromatography (TLC) was performed on prepared thin layers of E. Merck Silica gel-G on microscope slides. Visualization of the spots were effected by ultraviolet illumination or exposure to iodine vapour. Preparative TLC plates were prepared from a slurry of 20 g of E Merck Silica gel-G in 45 ml of water on 20 cm x 20 cm glass plates. The plates were dried at room temperature and activated at 120°C for 3 h prior to use. Column chromatography was performed using column chromatography grade silica gel (100-200 mesh).

Melting points (m.P) were determined in a Fisher-Johns melting point apparatus.

Elemental analyses were carried out in Coleman automatic carbon, hydrogen, nitrogen analyzers.

Infrared spectra were recorded on Perkin-Elmer model 1320 spectrophotometers and the absorption bands are reported in reciprocal centimeters (cm^{-1}).

Proton magnetic resonance (^1H NMR) spectra were recorded on a Jeol PMX-60 (60 MHz) and Bruker WM- 400 FT NMR (400 MHz) spectrometer and chemical shifts are reported in the scale as parts per million (ppm) down field from tetramethylsilane (TMS) which was used as an internal reference. Multiplicity is indicated using the following abbreviations br (broad), s (singlet), d (doublet), t (triplet) q (quartet), m (multiplet) etc. Coupling constants (J) are reported wherever necessary and are expressed in Hz.

Mass spectra were recorded on a Jeol JMS-300D Mass spectrometer at an electron beam energy of 70 eV and the peak positions of the principal fragments have been reported in m/z.

For recording $[\alpha]^{25}_{D}$ value of optically active compound JASCO DIP-370 digital polarimeter was used at the wavelength of the sodium D-line (589 nm) and at ambient temperature.

Enantiomeric purity of chiral alcohol was determined by preparing Mosher's ester of it and analysing the ^1H NMR spectrum (400 MHz) of the ester.

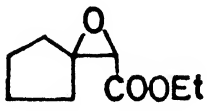
Optical purity of chiral acetate was determined by analysing the ^1H NMR spectrum (400 MHz), of the chiral acetate in the presence of the shift reagent (+) $Eu(hfc)_3$.

I.5 General procedure for the preparation of glycidic esters[54] 118 (a-e)

Procedure -A.

To a suspension of sodium sand (253 mg, 11 mg atom) in 3.5 ml of anhydrous xylene was slowly added a mixture of a ketone (10 mmol) and ethyl chloroacetate (1.25 g, 10.2 mmol) with stirring and cooling in an ice-salt bath. The reaction mixture was then allowed to come to room temperature during 1 hr and stirred at room temperature for additional 6 hr. The red coloured solution was then poured into 10 ml of ice cold water and extracted with ether (3 x 25 ml). The combined ether layer was washed with water (2 x 10 ml), brine (10 ml) and dried over anhydrous Na_2SO_4. After removal of ether using rotary evaporator, xylene was removed under reduced pressure. The crude product was purified by Kugelrhor distillation. The properties of the glycidic esters prepared by this procedure are as described below:

Ethyl-1 - oxaspiro-[2,4] - heptan -2- carboxylate (118 a)



Yield - 37%

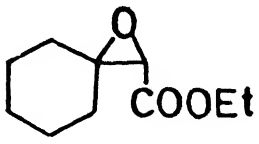
A clear liquid

B.P. : 100°C/4 mm (Lit[55] b.p. 72°C/1 mm)

IR spectrum (neat) ν_{max} : 1745 and 1725 (-C(=O)-OEt, glycidic) cm^{-1}

^1H NMR spectrum (CCl_4): 4.2 (2H, q, $-OCH_2CH_3$, J = 7Hz), 3.35 (1H,s, ), 2.1 - 1.43 (8H, m, 4 methylenes) and 1.27 (3H,t, $-OCH_2CH_3$, J = 7Hz)

Ethyl- 1 - oxaspiro [2,5] - octan-2-carboxylate (118 b)



Yield : 54%

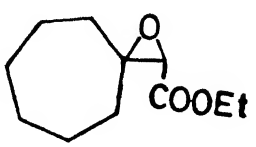
A semi-viscous liquid

B.P. : 100°C/2 mm (Lit[55] b.p. 90°C/1.5 mm)

IR spectrum (neat) ν_{max} : 1750 and 1725 (-C(=O)-OEt, glycidic) cm^{-1}

^1H NMR spectrum (CCl_4). δ4.2 (2H, q, $-OCH_2CH_3$, J = 7Hz), 3.12 (1H, s, ), 1.97 - 1.47 (10H, m, 5 methylenes) and 1.3 (3H, t, $-OCH_2CH_3$, J = 7 Hz).

Ethyl- 1 - oxaspiro-[2,6] -nonan - 2- carboxylate (118 c)



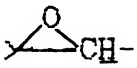
Yield : 40%

A clear oil.

B.P. : 105°C/1 mm (Lit[55] b.p. 90°C/ 1 mm)

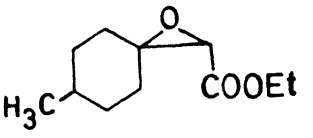
IR spectrum (neat) ν_{max}: 1750 and 1725 (-C(=O)-OEt, glycidic) cm^{-1}

^1H NMR spectrum (CCl_4): δ 4.17 (2H, q, $-OCH_2CH_3$, J = 7Hz),

3.1 (1H, s, ), 2.0 - 1.47 (12H, m, 6 methylenes) and

1.3 (3H, t, $-OCH_2CH_3$; J = 7 Hz)

Ethyl- 1 - oxaspiro-[2,5]- octan-5-methyl -2- carboxylate (118 d)



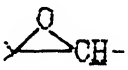
Yield - 57%

A clear liquid

B.P. : 115 - 170°C/ 10 mm.

IR Spectrum (neat) ν_{max}: 1725, 1750 (-C(=O)-OEt), glycidic) cm^{-1}

^1H NMR Spectrum (CCl_4): δ 4.2 (2H, q, J = 7 Hz, $-OCH_2-$),

3.03 - 3.1 (1H, 2s, ), 2.1 - 1.2 (1SH, m,

methylenes, methines and methyl triplet of $-O-C(=O)-CH_3$ at 1.3)

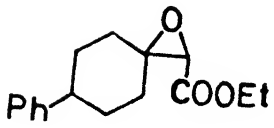
0.95 (3H, d, $HC-CH_3$)

Mass spectrum (m/z): 198 (M^+)

Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.6; H, 9.04; Found: C, 67.1;

H, 9.38%

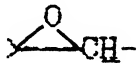
Ethyl-1-oxaspiro- [2,5] - octan-5-phenyl-2- carboxylate (118 e)



Yield : 56%

Thick liquid

IR Spectrum (neat) ν_{max} : 1725, 1750 (-C-OEt, glycidic) cm^{-1}

^1H NMR Spectrum (CCl_4): δ 7.0 (5H, s, aromatic protons), 4.2 (2H, q, $-OCH_2$, J = 7Hz), 3.13 - 3.16 (1H, 2s, ), 2.15 - 1.65 (9H, methylenes and -CH(Ph)), 1.3 (3H, t, J = 7 Hz, $-OCH_2CH_3$);

Mass spectrum (m/z): 260 (M^+)

Anal. Calcd. for $C_{16}H_{20}O_3$; C, 73.85; H, 7.69; Found: C, 74.1; H, 8.31%

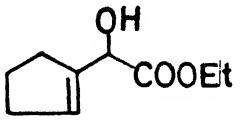
I.6 Isomerisation of glycidic esters [118 (a-e)] to α - hydroxy β,γ unsaturated esters[53]: [119 (a-e)]

General procedure

To a solution of a glycidic ester (1 mmol) in 1 ml of anhydrous dichloromethane was added BF_3, Et_2O (7.1 mg, 0.5 mmol) under dry N_2 atmosphere at 0°C. The reaction mixture was stirred at that temperature for 10 min. It was then neutralised with saturated $NaHCO_3$ solution and extracted with diethyl ether (4 x 15 ml). The combined ether layer was washed with brine (10 ml)

and dried over anhydrous Na_2SO_4. Removal of the solvent gave a thick oil, which was purified by column chromatography [eluent: pet ether [60-80°C]: ethyl acetate (94:6). The characteristics of isomerised products are described below:

Ethyl [2-hydroxy- (1-cyclopentenyl)] acetate (119 a)



Yield - 60%

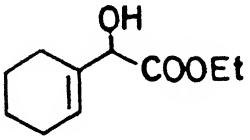
Thick oil (Lit.[55] b.p. 105-107°C/10 mmol)

IR spectrum (neat) ν_{max}: 3460 (br, O-H) and 1730 (-C(=O)-OEt) cm^{-1}

^1H NMR spectrum (CCl_4): δ 5.75(1H, br, s, =CH-), 4.7(1H,br,s,-CHOH), 4.25 (2H, q, $-OCH_2CH_3$, J = 7Hz) 3.05 (1H, br s, OH) 2.7-1.5 (6H, m, allylic and other methylenes) and 1.35 (3H, t,$-OCH_2CH_3$, J = 7Hz)

Mass spectrum (m/z): 170 (M^+), 97 ($M^+ - CO_2Et$).

Ethyl [2-hydroxy-(1-cyclohexenyl)] acetate (119 b)



Yield 65%

Thick oil (Lit[55] b.p. 116-8°C/10 mm)

IR spectrum (neat) ν_{max} : 3480 (br,-OH) and 1730 (C(=O)-OEt) cm^{-1}

^1H NMR spectrum (CCl_4) : δ 5.83(1H, br, s, = CH-) 4.6 - 4.1

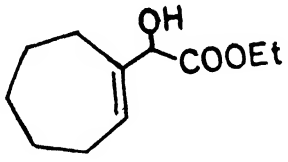
(3H, m, - CHOH and the $-OCH_2CH_3$, quartet, J = 7 Hz)

3.1 (1H, br, s, -OH) 2.4 - 1.97 (4H, m, allylic methylenes),

1.9 - 1.3 (4H, m, 2 methylenes) and 1.3 (3H, t,$-OCH_2CH_3$, J=7 Hz),

Mass spectrum (m/z) : 184 (M^+), 111 (M^+-COOEt),

Ethyl [2 -hydroxy - 2(1-cycloheptenyl)] acetate (119 c)



Yield 38%

Thick oil (Lit[55] b.p. 89°C/0.5 mm)

IR spectrum (neat) ν_{max}: 3500 (br) O-H), and 1730 (-C(=O)-OEt)cm^{-1}

^1H NMR spectrum (CCl_4): δ 5.93(1H, t,=CH-, J = 6Hz).

4.5-4.05 (3H, m, CH OH and the $-OCH_2CH_3$ quartet, J = 7Hz)

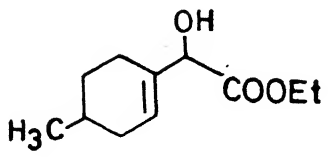
2.97 (1H, br. s, -OH), 2.45-1.97 (4H, m, allylic methylenes),

1.9-1.17(9H, m, 3 methylenes containing the $-OCH_2CH_3$

triplet, J = 7 Hz).

Mass spectrum (m/z) : 198 (M^+), 125 (M^+-CO_2Et)

Ethyl [2-hydroxy-2(4-methyl-1-cyclohexenyl)] acetate (119 d)



Yield 58%

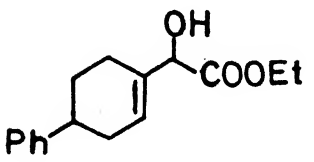
Thick liquid

IR spectrum (neat) ν_{max}: 1780 (br.-O-H) and 1720 (-C(=O)-OEt) cm^{-1}

^1H NMR spectrum (CCl_4): δ 5.6(1H, br. s,=CH-), 4.15-3.75 (3H, m, -CHOH and the $-OCH_2CH_3$ quartet, J=7 Hz). 2.8 (1H, br. s, -OH), 2.5-1.53 (7 H, m, methylenes and $CH(CH_3)$ methine), 1.27 (3H, t, $-OCH_2CH_3$, J = 7 Hz), 0.97 (3H, d, $-CH\ CH_3$, J = 3 Hz).

Mass spectrum (m/z): 198 (M^+), 125 (M^+-CO_2Et)

Ethyl [2-hydroxy-2(4-phenyl-1-cyclohexenyl)] acetate (119 e)



Yield 40%

M.P. 58°C

White crystalline solid which is crystallised from ethyl alcohol

IR spectrum (KBr) ν_{max}: 3440 (br.-O-H) and 1720 (-C(=O)-OEt) cm^{-1}

^1H NMR spectrum (CCl_4): δ 7.1 (5H, s, aromatic protons), 5.75 (1H. Br. s, = CH), 4.46-3.73 (3H, m,-CHOH and the $-O-CH_2-CH_3$ quartet, J = 7 Hz), 3.1 (1H, br. s, -OH), 2.2-1.5 (7H, m, methylenes and -CHPh methine), 1.3 (3H, t, $-OCH_2CH_3$, J= 7Hz).

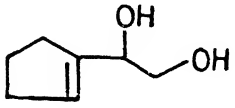
Mass Spectrum (m/z): 261 $(M + 1)^+$, 188 $[(M^+ + 1) - CO_2Et]$

I.7 $LiAlH_4$ reduction of isomerised hydroxy esters to the corresponding diols: [120 (a-e)].

General procedure:

To a suspension of $LiAlH_4$ (2.5 mmol) in anhydrous THF (5 ml) was slowly added a solution of the β,γ - unsaturated hydroxy ester at 5°C. After, the completion of addition ice bath was removed and then the solution was refluxed for 4 hr. Excess of $LiAlH_4$ was destroyed with ethyl acetate (20 ml) followed by water 1 ml and aq NaOH (1 ml). It was then filtered through a pad of anhydrous Na_2SO_4 and the residue thoroughly washed with ethyl acetate. The combined filtrate upon concentration yielded a thick oil which was purified by column chromatography (eluent: ethylacetate/pet ether: 25:75) to yield the diol. The characteristics of diols [**120 (a-e)**] are given below:

1-Cyclopentene-1-(β-hydroxy-ethanol) (120 a)



Yield 48%

Thick oil.

IR spectrum (neat) ν_{max} : 3400 (-OH) cm^{-1}

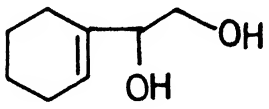
^1H NMR spectrum (CCl_4): δ 5.5 (1H, br. s, -CH = C<),

4.4-3.56 (3H, m, -CHOH-CH_2OH), 3.53-3.3 (2H, br. s, -CHOH-CH_2OH),

2.5-1.35 (6H, m, allylic and other methylenes).

Mass spectrum (m/z): 128 (M^+), 110 (M^+-H_2O), 81 (M^+-CHO)

1-Cyclohexene-1-(β-hydroxy-ethanol) (120 b)



Yield 67%

Colourless viscous oil

IR spectrum (neat) ν_{max}: 3500 (-OH) cm^{-1}

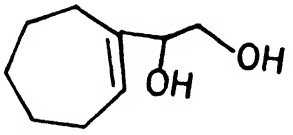
^1H NMR spectrum (CCl_4) : δ5.6 (1H, br., s, -CH = C<),

4.5-3.6 (3H, m, CHOH - CH_2OH), 3.53 - 3.16 (2H, m, CHOH - CH_2OH)

2.3- 1(8 H, m, allyl and other methylenes)

Mass spectrum (m/z): 143 $(M + 1)^+$, 112 [$(M^+ + 1)$ - CH_2OH]

1-Cycloheptene-1-(β-hydroxy-ethanol) (120 c)



Yield 70%

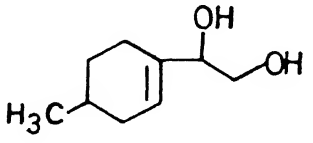
Light green coloured viscous liquid

IR spectrum (neat) ν_{max} : 3460 (-OH) cm^{-1}

^1H NMR spectrum (CCl_4): δ 5.83 (2H, t, -C<u>H</u> = C<), 4.16-3.88 (2H, m, C<u>H</u>OH-C<u>H</u>$_2$OH) 3.69-3(3H, m, CHO<u>H</u> - CH$_2$O<u>H</u>) 2.5-1 (10H, m, allylic and other methylenes)

Mass spectrum (m/z): 156 (M^+), 138 (M^+-H_2O)

4-Methyl-1-cyclohexene-1 (β-hydroxy ethanol)(120d)



Yield 52%

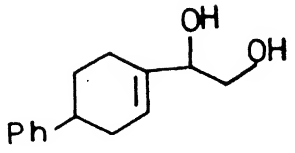
A viscous liquid

IR spectrum (neat) ν_{max}: 3465 (-OH) cm^{-1}

^1H NMR spectrum (CCl_4) : δ 5.56 (1H, br. s - C<u>H</u> = C <), 4.6 - 3.8 (3H, m, -C<u>H</u>OH - C<u>H</u>$_2$OH) 3.66 - 3.16(2H, m, -CHO<u>H</u> -CH$_2$O<u>H</u>) 2.5-1.06(7H, m, allyl and other methylene and methines) 1.00 - 0.66(3H, d, >CH(C<u>H</u>$_3$))

Mass spectrum (m/z): 156 (M^+), 157 (M + 1)$^+$, 139 [(M^++1)-H_2O]

4-Phenyl-1-cycohexene-1-(β -hydroxy ethanol) (120e)



Yield 66%

White crystalline solid, crystallised from ethyl alcohol

m.p. 64°C

IR spectrum (KBr) ν_{max}: 3400 (-OH) cm^{-1}

^1H NMR spectrum (CCl_4): δ 7.16 (5H, s, aromatic protons), 5.66 (1H, br., s, -CH = C <) 4.16-3 (5H, m, -CHOH - CH_2OH) 2.15-1.00 (7H, m, allyl and other methelene, methine)

Mass spectrum (m/z): 219 $(M+1)^+$, 201 $[(M^++1)-H_2O]$, 172, 104

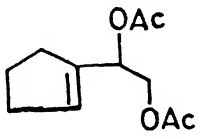
I.8 Preparation of acetyl derivatives [121 (a-e)] of diols [120 (a-e)]

General Procedure:

A mixture of a diol (0.5 mmol) and acetic anhydride (204 mg, 2 mmol) in 1 ml of anhydrous pyridine was stirred at room temperature for 20 hr. It was then poured into 10 ml ice cold water and extracted with ether (3 x 15 ml). The combined ether layer was washed with 5% HCl (5 ml), water (2 x 5 ml) and brine (5 ml) and dried over anhydrous Na_2SO_4. Removal of the solvent gave a crude product which was purified by column chromatography

(eluent: ethyl acetate/pet ether= 5/95) to obtain pure diacetate. The characteristics of diacetates [**121 (a-e)**] are given below:

1-(Cyclopent-1-ene)-1,2-diacetoxy ethane (121 a)



Yield 88%

The colourless thick liquid

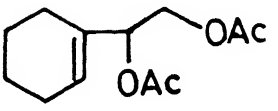
IR spectrum (neat) ν_{max}: 1750 (-O-CO-CH_3) cm^{-1}

^1H NMR spectrum (CCl_4): δ 5.73-5.3 (2H, m, = CH, - CHOAc), 4.15-3.8 (2H, m, -CH_2OAc), 2.45-1.3 (12H, m, allylic and other methylenes, with two-OCO-CH_3 singlets at δ 2.03 and δ 1.97

Mass spectrum (m/z): 152 (M^+-CH_3COOH), 92

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.26; H, 7.54; Found: C, 63.05; H, 7.65%

1-(Cyclohex-1-ene)-1,2-diacetoxy ethane (121 b)



Yield 95%

A clear thick liquid

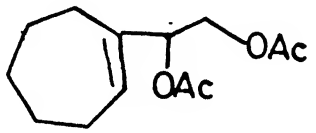
IR spectrum (neat) ν_{max} : 1745 (-O-C-CH_3) cm^{-1}
O

^1H NMR spectrum (CCl_4): δ 5.6(1H, br. s, - =CH), 5.3-5.00 (1H, q, - CH OAc), 4.66 - 3.75(2H, m, - CH_2 OAc), 2.3-1.35(14H, m, allylic and other methylenes, with two acetoxy (-O-CO-CH_3) singlets at δ 2 and δ 1.94)

Mass spectrum (m/z): 166 [$(M^+ +1)$-CH_3COOH], 106

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.72; H, 7.96; Found: C, 63.12; H, 7.09%

1-(Cyclohept-1-ene)-1, 2-diacetoxy ethane (121 c)



Yield 86%

A colourless viscous liquid

IR spectrum (neat) ν_{max} : 1745 (-O-CO-CH_3) cm^{-1}

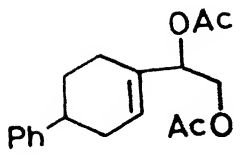
^1H NMR spectrum (CCl_4): δ 5.73-5.26 (2H, br., m, = CH, -CHOAc), 4.3-3.75 (2H, m, - CH_2OAc), 2.45-1.33 (16H, m, allylic and other methylenes and two-(O-CO-CH_3 singlets at δ 2.12 and δ 2.06

Mass spectrum (m/z): 241 $(M+1)^+$, 181 [$(M^+ +1)$-CH_3COOH].

Anal. Calcd. for $C_{13}H_{20}O_4$: C, 65.05; H, 8.3%

Found : C, 66.02; H, 8.9%

1-(4-Phenyl-cyclohex-1-ene)-1,2-diacetoxy ethane (121 e)



Yield 82%

Thick liquid

IR spectrum (neat) ν_{max} : 1735 ($-O-CO-CH_3$) cm^1

^1H NMR spectrum (CCl_4): δ 7.15 (5H, s, aromatic protons), 5.7 (1H, br. s, = CH), 5.4-5.1 (2H, m, -CHOAc) 4.3-3.75 (2H, m, $-CH_2OAc$), 2.45 - 0.78 (13H, m, allylic and other methylenes, methine and two ($-O-CO-CH_3$) singlets at δ 2.04 and δ 1.96 also.

Mass spectrum (m/z): 302 (M^+), 242 (M^+-CH_3COOH).

Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.52; H, 7.28; Found: C, 72.05; H, 7.36%

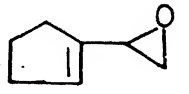
I.9 General procedure for the preparation of vinyl epoxides: [122 (a-e)]

To a stirred solution of a diol (1 mmol) in dry ether (2 ml) was added pyridine (1.5 mmol) and freshly recrystallised p-toluene sulphonyl chloride (1.2 mmol) at 0^oC. It was stirred at 0-10^oC for 7 days by the end of which the reaction was generally complete (TLC monitoring as indicator). Solvent was then removed under reduced pressure and the crude product so obtained was used without further purification.

A stirred suspension of NaH (1.2 mmol) in dry ether (2 ml) at $0^{\circ}C$ was treated with a solution of crude tosylate, obtained from the above mentioned reaction, in ether (2 ml). The reaction mixture was stirred at room temperature for 12 hr. It was then diluted with water (5 ml), and extracted with ether (3 x 10 ml). Evaporation of the solvent yielded a crude product which was purified by column chromatography. (eluent : pet ether/ether 90/10).

The characteristics of vinyl epoxides [**122 (a-e)**] are given below:

Oxirane-2-(cyclopent-1-ene) (122a)



Yield 87%

A clear liquid

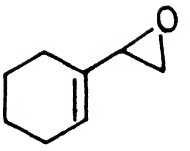
^1H NMR spectrum (CCl_4) : δ 5.75 (1H, t, =CH, J = 2Hz)

3.3(1H, t, -CH-CH_2), 2.83-2.6 (2H, m, CH-CH_2)

2.3 - 0.6 (6H, m, allylic and other methylenes)

Mass spectrum (m/z): 111 $(M+1)^+$, 110 (M^+)

xirane-2-(cyclohex-1-ene) (122 b)



ield 78%

. freely mixing colourless liquid

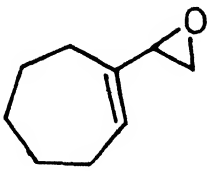
H NMR spectrum (CCl_4) : δ 5.75 (1H, t, =CH, J=3 Hz),

3.09 (1H, t, - CH-CH_2), 2.66-2.27 (2H, m, -CH-CH_2),

1.15-1.18 (8H, m, allyl and other methylenes)

lass spectrum (m/z): 125 $(M+1)^+$, 124 (M^+).

)xirane-2 (cyclohept-1-ene) (122 c)



Yield 75%

A clear liquid

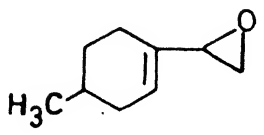
^{1}H NMR spectrum (CCl_4) : δ 5.7 (1H, t, =CH, J =6 Hz),

3.15 (1H, t, -CH-CH_2), 2.6-2.3 (2H, m, - CH-CH_2),

2.15-1.17 (10H, m, allyl and other methylenes)

Mass spectrum (m/z): 139 $(M+1)^+$, 138 (M^+).

Oxirane-2-(4-methyl-cyclohex-1-ene) (122 d)



Yield 81%

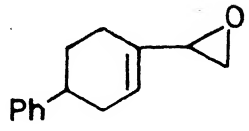
^{1}H NMR spectrum (CCl_4) : δ 5.9 (1H, br, s, = CH)

3.2 (1H, t, -CH(O)-CH_2, J = 3 Hz), 2.66-2.45 (2H, m, -CH(O)-CH_2),

1.78-0.75 (10H, m, allylic and other methylenes, methine with methyl doublet of - $CH(CH_3)$ at δ 0.97).

Mass spectrum (m/z): 139 $(M+1)^+$, 138 (M^+).

Oxirane-2-(4-phenyl-cyclohex-1-ene) (122 e)



Yield 71%

^{1}H NMR spectrum (CCl_4) : δ 7.3 (5H, br s, aromatic proton),

5.73 (1H, br., s, = CH), 2.96 (1H, t, -CH(O)-CH_2, J = 3 Hz),

2.83-2.6 (2H, m, - CH(O)-CH_2), 2.3-1.2 (7H, m, allylic and other methylenes and the methine proton).

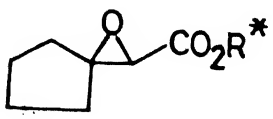
Mass spectrum (m/z): 201 $(M+1)^+$, 200 (M^+).

I.10 General procedure for the preparation of chiral glycidic esters: [147 (a-c)]

(a) Preparation of $ClCH_2COOR^*$: Choroacetic acid (1.1 mmol) was taken with (-) menthol (1 mmol) in 20 ml toluene. To it was added two drops of conc H_2SO_4. The solution was refluxed using Dean-Stark apparatus for 7 hr. After the completion of reaction it was neutralised with saturated sodium bicarbonate solution. Then it was worked up with ether (2x25 ml), water (2 x 5 ml), brine (5 ml). Finally after removal of ether toluene was removed under reduced pressure and the thick liquid obtained was pure $ClCH_2COOR^*$.

(b) Preparation of glycidic ester: Glycidic ester was prepared following the same procedure as is given in section I.6 and $ClCH_2COOR^*$ (where R^* is 1R, 2S, 5R (-) menthol) was used instead of $ClCH_2COOEt$. The properties of glycidic esters are given below:

Menthyl-1-oxaspiro-[2,4]-heptan-2-carboxylate (147a)



Yield 60%

Colourless thick liquid

IR spectrum (neat) ν_{max}: 1750, 1725 (-COOEt, glycidic)cm^{-1}

^1H NMR spectrum (CCl_4): δ 4.75-4.5 (1H, br m, >C(O)—CH-COOCH<),

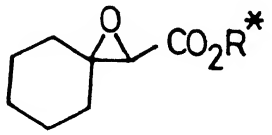
3.9 and 3.3 (1H, two singlets, relative areas ca 1:3, >C(O)CH-)

2.15-0.65 (26H, m, methylenes, methines and two sets of overlapping doublet due to menthylmethyl at δ 0.95 and δ 0.7 of J = 7 Hz)

Mass spectrum (m/z): 280 (M^+)

Anal. Calcd. for : $C_{17}H_{28}O_3$: C, 72.86; H, 10.0; Found: C, 72.23; H, 9.5%

Menthyl-1-oxaspiro- [2,5]-octan-2-carboxylate (147b)



Yield 64%

Colourless thick liquid

IR spectrum (neat) ν_{max} : 1750, 1725 (-COOEt, glycidic)cm^{-1}

^1H NMR spectrum: δ 4.65 - 4.45 (1H, br, m, >C(O)CH-COOCH<),

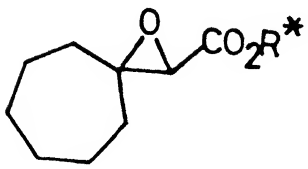
3.9 and 3.07 (1H, two singlets, relative areas ca 1:3, >C(O)CH-),

2.6 - 0.7 (28H, m, methyls and methines and two sets of overlapping doublets due to menthyl methyl at δ 0.8 and δ 0.73 of J = 7 Hz

Mass spectrum (m/z): 294 (M^+).

Anal. Calcd. for : $C_{18}H_{30}O_3$: C, 73.47; H, 10.2; Found: C, 73.12; H, 9.8%

Menthyl-1-oxaspiro- [2,5]-nonan-2-carboxylate (147c)



Yield 45%

Colourless viscous liquid

IR spectrum (neat) ν_{max} : 1750, 1725 (COOEt, glycidic)cm^{-1}

^1H NMR spectrum (CCl_4): δ 4.75-4.45 (1H, br. m, >C(O)CH-COOCH<),

3.15 (1H, s, >C(O)CH-) 2.4-0.65 (30H, m, methylenes and methines, and two sets of overlapping doublets due to menthyl methyl at δ 0.85 and δ 0.73 of J = 7 Hz

Mass spectrum (m/z): 308 (M^+).

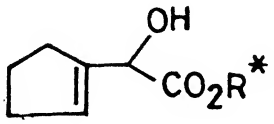
Anal. Calcd. for : $C_{19}H_{32}O_3$: C, 74.03; H, 10.39;

Found: C, 73.82; H, 9.4%

I.11 Isomerisation of glycidic esters [147 (a-c)] to α-hydroxy - β,γ -unsaturated esters[53] [148 (a-c)]

The isomerisation procedure is same as given in lit.[53]. The characteristics of isomerised products are given below.

Menthyl-2 hydroxy-2- [cyclopent-1-ene]-acetate (148a)



Yield 22%

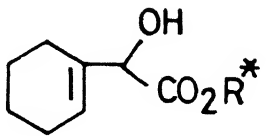
Colourless liquid

IR spectrum (neat) ν_{max} : 3500, 1720 (-OH, -COOEt)

^{1}H NMR spectrum (CCl_4): δ 5.67 (1H, br. s, = C<u>H</u>),
5-4.33 (2H, br. m, -COOC<u>H</u> < and CHO<u>H</u>) 2.75 (1H, br. s, O<u>H</u>),
2.3-0.65 (24H, m, methylenes and methines, and
overlapping doublets due to menthyl methyles)

Mass spectrum (m/z): 280 (M^+), 142, 138.

Menthyl-2-hydroxy-2- [cyclohex-1-ene]-acetate (148b)



Yield 65%

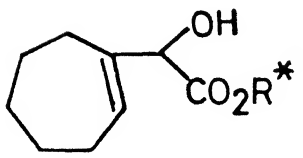
Thick liquid

IR spectrum (neat) ν_{max}: 3500, 1715 (-OH, COOEt)cm^{-1}

^{1}H NMR spectrum (CCl_4): δ 5.8 (1H, br. s, = C<u>H</u>),
4.8-4.45 (1H, br. m, - COOC<u>H</u>), 4.1 (1H, br. s, -C<u>H</u>OH),
2.97 (1H, br. s,-O<u>H</u>), 2.6-0.6 (26H, m, methylenes, methines,
and overlapping doublets due to menthyl methyl
protons.

Mass spectrum (m/z): 294 (M^+), 156, 138

Menthyl-2-hydroxy-2- (cyclohept-1-ene) acetate (148c)



Green coloured thick liquid

IR spectrum (neat) ν_{max} : 3500, 1710 cm^{-1}

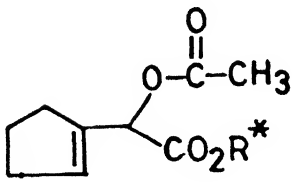
^1H NMR spectrum (CCl_4): δ 5.75(1H, t, = C<u>H</u>, J = 6 Hz), 4.75-4.45 (1H, br. m, -COOC<u>H</u><), 4.3(1H, br.s, -C<u>H</u>OH), 2.75(1H, br.s, -O<u>H</u>), 2.4-0.75(28H, m, methylenes, methines and overlapping doublets due to menthyl methyl protons.

Mass spectrum (m/z): 308 (M^+), 170, 138

I.12 General Procedure for the preparation of acetyl derivatives [149 (a-c)]

A mixture of a hydroxy compound (0.5 mmol), acetic anhydride (204 mg, 2 mmol) and anhydrous pyridine (0.05ml, 0.6 mmol) in 2 ml of dry dichloromethane was stirred at room temperature for 20 hr. It was then poured into 10 ml of ice cold water and extracted with CH_2Cl_2 (3 x 15 ml). The combined CH_2Cl_2 layer was washed with 5%, HCl (10 ml), water (2 x 5 ml), brine (10 ml) and dried over anhydrous Na_2SO_4. Removal of the solvent gave a crude product which was purified by column chromatography [eluent: pet ether (60-80°C): ethyl acetate (97:3)]. The properties of the α-acetoxy- β,γ -unsaturated esters are given below.

Menthyl-2-acetoxy-2- (cyclopent-1-ene) acetate (149a)



A mobile colourless liquid

Yield 85%

IR spectrum (neat) ν_{max} : 1740 (-O-CO-CH_3, R^*-O-C=O) cm^{-1}

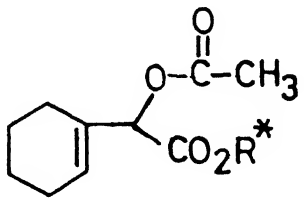
^1H NMR spectrum (CCl_4): δ 5.78 (1H, br. s, = C<u>H</u>),

5.4 and 5 (1H, 2s, relative area ca 1:3, -C<u>H</u>OAC),

4.79-4.3 (1H, br. m, -CO_2C<u>H</u><), 2.45-0.4 (27H, m, allyl and other methylenes, methines and include -O-CO-CH_3 methyl peak at δ 2.25 and overlapping menthyl methyl doublets at δ 0.95, δ 0.8 and δ 0.68)

Mass spectrum (m/z): 322 (M^+), 323 $(M+1)^+$, 279 (M^+-43)

Menthyl-2-acetoxy-2- (cyclohex-1-ene)-acetate (149b)



A clear liquid

Yield 92%

IR spectrum (neat) ν_{max}: 1735 (-O-CO-CH_3, R^*-O-C=O) cm^{-1}

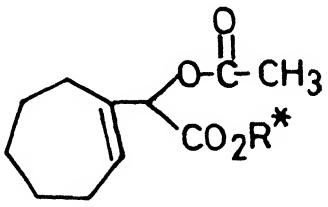
^1H NMR spectrum (CCl_4): δ 5.83(1H, br.s, = C<u>H</u>),

5(1H, s, -C<u>H</u>OAc), 4.75-4.3 (1H, br.m, -CO_2C<u>H</u><),

2.38-0.45 (26H, m, allylic and other methylenes and three overlapping menthyl methyl doublets at δ 0.95, 0.79 and 0.62), 2.12 and 2.03 (3H, 2s, relative area Ca 1:3, $-OCOCH_3$).

Mass spectrum (m/z): 336 (M^+), 337 $(M+1)^+$, 293 (M^+-43)

Menthyl-2-acetoxy-2-(cyclohept-1-ene)-acetate (149c)



A clear liquid

Yield 82%

IR spectrum (neat) ν_{max}: 1740 ($-O-CO-CH_3$, $-R^*-O-C=O$) cm^{-1}

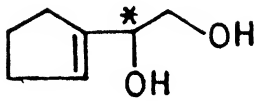
^1H NMR spectrum (CCl_4): δ 5.8 (1H, t, =CH), 4.7 (1H, s, -CHOAc), 4.6-4.3(1H,m,-O-CH<), 2.3-0.45(28H, m, allylic and other methylenes and overlapping doublets at δ 0.95, 0.8 and 0.63), 2.07 and 2.0 (3H, 2s, relative area ca 1:3, $-OCOCH_3$)

Mass spectrum (m/z): 351 $(M+1)^+$, 290 $[(M^+ +1)-59]$

I.13 $LiAlH_4$ reduction of the hydroxy esters [148 (a-c)] to chiral diol [150 (a-c)]

The procedure for $LiAlH_4$ reduction was followed as described in section I.7. The characteristics of diols are given below:

2-(Cyclopent-1-ene)-2-hydroxy ethanol (150a)



Yield 77%

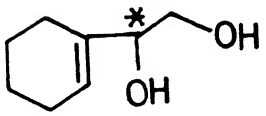
A colourless thick liquid

IR spectrum (neat) ν_{max} : 3465 (-OH) cm^{-1}

^1H NMR spectrum (CCl_4) : δ 5.5(1H, br.s, -CH= C<), 4.3-4 (3H, m, -CHOH-CH_2OH) 3.5-3(2H, m,-CHOH-CH_2OH) 2.5-1 (6H, m, allyl and other methylenes)

Mass spectrum (m/z): 128 (M^+), 110 (M^+-H_2O), 81

2-(Cyclohex-1-ene)-2-hydroxy ethanol (150b)



Yield 85%

A viscous oil

IR spectrum (neat) ν_{max} : 3460 (-OH) cm^{-1}

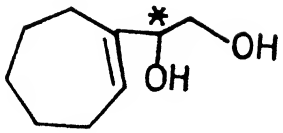
^1H NMR spectrum (CCl_4) : δ 5.90 (1H, br.s, -CH = C<)

4.5-4.1(3H, m, - CHOH -CH_2OH) 3.8-3.2 (2H, m,-CHOH - CH_2OH)

2.5-2.2(4H, m, allylic methylenes), 2-1.8(4H, m, other methylenes)

Mass spectrum (m/z): 143 $(M+1)^+$, 112 $[(M^++1)-CH_2OH]$

2-(Cyclohept-1-ene)-2-hydroxy ethanol (150c)



Yield 82%

A thick oil

IR spectrum (neat) ν_{max} : 3455 (-OH) cm^{-1}

^1H NMR spectrum (CCl_4) : δ 5.66(1H, t, -CH = C<)

4.15-3.6(3H, m, CHOH-CH_2OH) 3.56-3(2H, m, -CHOH CH_2OH)

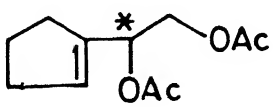
2.5-1(10H, m, allyl and other methylenes).

Mass spectrum (m/z): 156 (M^+), 138 (M^+-H_2O)

I.14 General procedure for the preparation of diacetates: [151 (a-c)]

The procedure for acetylation of diols is given in section I.8. The spectral analysis of diacetates are given below:

Diacetate 151a



Yield 79%

A thick liquid

IR spectrum (neat) ν_{max} : 1735 (-O-CO-CH_3) cm^{-1}

^1H NMR spectrum (CCl_4): δ 5.88 - 5.3(2H, m, = CH, -CHOAC),

4.26-3.8(2H, m, -CH_2OAc) 2.6-1 (12H, m, allylic and

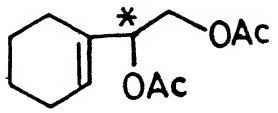
other methylenes and two -O-CO-CH_3 methyl peaks at δ 2.06 1.97)

Mass spectrum (m/z): 152 (M^+-CH_3COOH), 92

$[\alpha]_D^{25}$.(-) 39.04 (C1, $CHCl_3$)

Anal. Calcd. for : $C_{11}H_{16}O_4$: C, 62.26; H, 7.56; Found: C, 63.02; H, 7.67%

Diacetate (151b)



Yield 60%

A clear liquid

IR spectrum (neat) ν_{max} : 1740 (-O-CO-CH_3) cm^{-1}

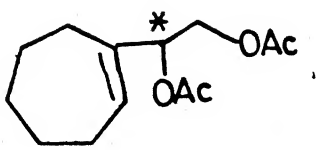
^1H NMR spectrum (CCl_4): δ 5.75(1H, br. s, = C<u>H</u>), 5.15(1H, q, -C<u>H</u>OAc, J = 5 Hz) 4.3-3.75(2H, m, -$C\underline{H}_2$OAc), 2.26-1.3 (14H, m, methylenes and two-O-CO-$C\underline{H}_3$ methyl peaks at δ 2.03 and 1.99)

Mass spectrum (m/z): 166 (M^+-CH_3COOH), 106

$[\alpha]_D^{25}$: (-) 36.80 (C1, $CHCl_3$)

Anal. Calcd. for: $C_{12}H_{18}O_4$: C, 63.72; H, 7.96; Found: C, 63.23; H, 7.47%

Diacetate (151c)



Yield 78%

A semi-viscous liquid

IR spectrum (neat) ν_{max} : 1735 ($-O-CO-CH_3$) cm^{-1}

^1H NMR spectrum (CCl_4) :δ5.75(1H, t, = C<u>H</u>, J = 6 Hz), 5.3-5.0 (3H, m, -C<u>H</u>(OAc), CH_2(OAc), 2.3-1.15(16H, m, allylic and other methylenes and two-O-CO-CH_3 methyl peaks at δ 2.03 and 1.95 also)

Mass spectrum (m/z): 240 (M^+), 180 (M^+-CH_3COOH)

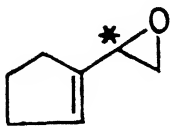
$[\alpha]_D^{25}$: (-) 35.67 (C1, $CHCl_3$)

Anal. Calcd. for : $C_{13}H_{20}O_4$: C, 65.00; H, 8.33; Found: C, 64.09; H, 9.01%

I.15 Chiral vinyl Epoxide [152 (a-c)]

Procedure for the synthesis of vinyl epoxide is given in the section I.9. The characteristics of vinyl epoxides are given below.

Oxirane-2-(cyclopent-1-ene) (152a)



Yield 59%

A clear liquid

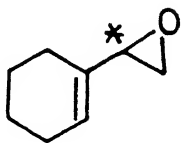
$[\alpha]_D^{25}$: (-) 1.23 (C1, $CHCl_3$)

^1H NMR spectrum (CCl_4): δ 5.74(1H, br. t, = C<u>H</u>-), 3.3(1H, t, -C<u>H</u>(O)-CH_2, J = 3 Hz), 2.83-1.6 (8H, m, methylenes of oxirane

and cyclopentane rings),

Mass spectrum (m/z): 111 $(M + 1)^+$, 110 (M^+)

Oxirane-2-(cyclohex-1-ene) (152b)



Yield 79%

A colourless liquid

$[\alpha]_D^{25}$: (-) 4.64(C1, $CHCl_3$)

^1H NMR spectrum (CCl_4): δ 5.75(1H, br. t, =CH-), 3.15 (1H, t,

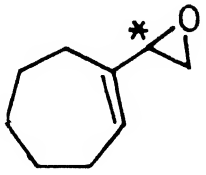

, J = 3 Hz), 2.73-2.35(2H, m,

),

2.3-0.75(8H, m, allylic and other methylenes)

Mass spectrum (m/z): 125 $(M+1)^+$, 124 (M^+)

Oxirane-2-(cyclohept-1-ene) (152c)



Yield 82%

A clear liquid

$[\alpha]_D^{25}$: (-) 5.48(C1, $CHCl_3$)

^1H NMR spectrum (CCl_4) : δ 5.83(1H, t, = CH, J = 6 Hz),

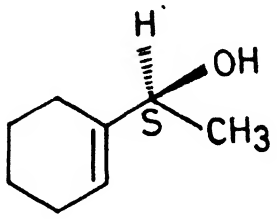
3.15(1H, q, -CH(O)CH$_2$, J = 2 Hz), 2.76-1.16(12H, m, oxirane and cycloheptane ring methylenes)

Mass spectrum (m/z): 139$(M+1)^+$, 138 (M^+)

I.16 Determination of absolute configuration of vinyl epoxide (152b)

To a suspension of $LiAlH_4$ (2 equiv) in dry THF (3 ml) was slowly added a solution of **152b** (248 mg: 2 mmol) in THF at 0-5°C. The solution was allowed to stir for 4 hr at room temperature and then it was worked up following the general work up procedure for $LiAlH_4$ reduction reaction (vide section I.7). The crude product was purified by column chromatography (eluent: ether/petether: 5/95) to obtain pure **153**.

1-(Cyclohex-1-ene) ethanol (153)



Yield 70%

A mobile liquid

IR spectrum (neat) ν_{max} : 3400 (-OH) cm^{-1}

^1H NMR spectrum (CCl_4): δ 5.52 (1H, br s, = CH), 4.11 (1H, q, -CHOH, J = 6 Hz), 2.12-1.39 (9H, m, -OH and methylenes), 1.22 (3H, d, -CH(CH_3), J = 6 Hz)

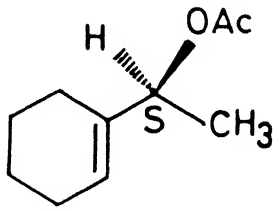
$[\alpha]_D^{25}$: (-) 6.88 (C1, $CHCl_3$) observed

$[\alpha]_D^{25}$: (-) 9.8 (C1, $CHCl_3$) Lit[63]

Acetylation of (-)(153)

The procedure followed for acetylation of **153** was same as described in section I.12.

Compound (154)



Yield 90%

A colourless oil

IR spectrum (neat) ν_{max} : 1750 ($-O-CO-CH_3$) cm^{-1}

^1H NMR spectrum (CCl_4) : δ 5.6 (1H, br s, = CH), 4.96 (1H, q, -CH(OAc), J = 7 Hz), 2.15-1.4 (11H, m, four methylenes and a singlet at δ 2.03 for $-O-COCH_3$), 1.33 (3H, d, $-CH(CH_3)$, J = 7 Hz)

$[\alpha]_D^{25}$ (-) 14.355 (C1, $CHCl_3$)

e.e (by using shift reagent): 50%

I.17 General Procedure for the preparation of glycidic esters: (181, 184, 187):

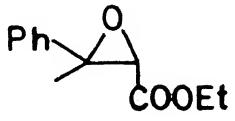
Glycidic ester **181** was prepared following the procedure (B).

Procedure (B) : In this procedure[75] instead of sodium potassium was used. In a two neck round bottom flask fitted with a dropping funnel in its one neck the acetophenone (10 mmol, 1.2g) was charged with freshly distilled ethyl

chloroacetate (1.25 g, 10.2 mmol). A solution of 394 mg of potassium in 8.50 ml of dry t-butyl alcohol was introduced into the dropping funnel and the system was evacuated and filled with argon. The t-butoxide was dropped in over an hour with stirring, while the temperature was maintained at 15-20°C by cooling the flask with an ice water bath. After the addition was completed the mixture was stirred for additional 5 hr. at room temperature. Most of the t-butyl alcohol was removed at reduced pressure and the residue was taken up in ether. The ether solution was washed with water, followed by brine solution and finally dried over anhydrous sodium sulfate. After removal of ether at rotary evaporator, the crude product was purified by Kugelrhor distillation or by column chromatography.

Glycidic esters **184** and **187** were synthesised by following procedure (A) as mentioned in section I.5.

Ethyl- 3- phenyl- 2,3-epoxy butanoate :(181)



Yield 60%

A light yellow coloured oil

b.p : 105°C/ 5 mm (Lit[76] 111-114°C/ 3 mm)

IR spectrum (neat) ν_{max} : 1730, 1750 (glycidic, -COOEt) cm^{-1}

^1H NMR spectrum (CCl_4): δ 7.15(5H, s, aromatic protons),

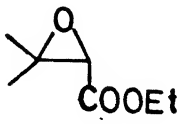
4.25 and 3.69 (2H total two q, J= 7 Hz and J = 6.5 Hz respectively (relative areas, ca. 1:1) $-O-\underline{CH}_2-CH_3$) ,

3.45 and 3.24 (1H, two m, $>C\overset{O}{\diagup\!\diagdown}\underline{CH}-$, J = 6 Hz),

1.66 and 1.41 (3H, two s, $-(H_3C)C\overset{O}{\diagup\!\diagdown}CH-$),

1.29 and 0.86 (two t, J = 7 and J = 6.5 Hz respectively, (relative areas ca. 1:1) $-O-CH_2\underline{CH}_3$)

Ethyl-3-methyl-2,3-epoxy butanoate : (184)



Yield 52%

A clear liquid

b.p : 90°C/30 mm (Lit[77] 163-168°C/760 mm)

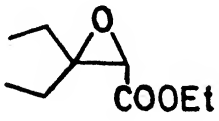
IR spectrum (neat) ν_{max} : 1730, 1755 (glycidic, - COOEt) cm^{-1}

^1H NMR spectrum (CCl_4): δ 4.12(2H, q, $-O\underline{CH}_2CH_3$, J = 7 Hz),

3.09(1H, s, $>C\overset{O}{\diagup\!\diagdown}\underline{CH}-$), 1.36 and 1.3(3H, two s, $\underline{H}_3C-C-C\underline{H}_3$)

1.15(3H, t, $-OCH_2-C\underline{H}_3$)

Ethyl-3-ethyl-2,3-epoxy pentanoate : (187)



Yield 48%

Colourless thick oil

IR spectrum (neat) ν_{max}: 3500, 1720 (-OH, -COOEt) cm^{-1}

^1H NMR spectrum (CCl_4) : δ 7.03(5H, s, aromatic protons),

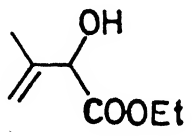
5.15(2H, s, =C<u>H</u>-), 4.69(1H, br. s, - C<u>H</u>OH),

3.95(2H, q, -O-C<u>H</u>$_2$-CH$_3$), 3.00 (1H, br. s, -O<u>H</u>),

1.01 (3H, t, -OCH$_2$-C<u>H</u>$_3$)

Mass spectrum (m/z): 206 (M^+), 133 (M^+-CO_2Et)

Ethyl-2-hydroxy-3-methyl-3-butenoate : (185)



Yield 35%

Labile liquid with no colour

b.p : 70°C/10 mm (Lit[79] 68-69°C/10 mm)

IR spectrum (neat) ν_{max} : (3460, 1730) (-OH, -COOEt) cm^{-1}

^1H NMR spectrum (CCl_4): δ 5.2-4.7(2H, m, =C<u>H</u>-),

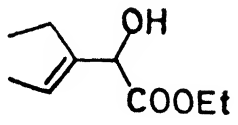
4.5 (1H, s, -C<u>H</u>OH,), 4.13 (2H, q, -OC<u>H</u>$_2$CH$_3$, J = 7 Hz),

3.18 (1H, br, s, -O<u>H</u>), 1.63 (3H, m, =C(C<u>H</u>$_3$)——CH<),

1.25 (3H, t, -OCH$_2$C<u>H</u>$_3$)

Mass spectrum (m/z): 145 $(M+1)^+$, 71 (M^+-CO_2Et)

Ethyl-3-ethyl--2-hydroxy-3-pentenoate : (188)



Yield 50%

Freely moving liquid

b.p : 83°C/6 mm (Lit[55] 80-81°C/5 mm)

IR spectrum (neat) ν_{max} : 3500, 1715 (-OH, -COOEt) cm^{-1}

^1H NMR spectrum (CCl_4): δ 5.35(1H, br, q, =C<u>H</u>-, J = 5.7 Hz),
4.82 and 4.28(1H, broadened singlets, relative area ca 2.1, >C<u>H</u>OH), 4.03(2H, q, $-OC\underline{H}_2CH_3$, J = 7 Hz),
3.33 (1H, brd, -O<u>H</u>), 1.92(2H, t, $CH_3-C\underline{H}_2-C = CH$, J = 7 Hz),
1.59 and 1.53 (3H, 2d, relative areas ca. 2:1, $\underline{H}_3C-C=$)
1.20(3H, t, $C\underline{H}_3-CH_2-C = CH$, J = 7 Hz), 0.90(3H, t,
$-OCH_2C\underline{H}_3$, J = 7 Hz),

Mass spectrum (m/z): 171 (M^+), 98 (M^+-CO_2Et)

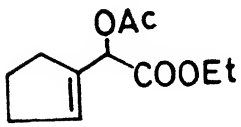
I.19 Acetylation of ∝ - hydroxy - β,γ -unsaturated esters [119 (a-e), 182, 185, 188]

A mixture of hydroxy compound (0.5 mmol), acetic anhydride (204 mg;2 mmol) and 0.05 ml of anhydrous pyridine was taken in 5 ml dry dichloromethane. This reaction mixture was stirred at room temperature for 20 hr. It was then extracted with ether (3x15 ml) and the combined ether layer was washed with 5% HCl (5 ml), water (2x5 ml), brine (10 ml) and dried over anhydrous Na_2SO_4. Removal of the solvent gave a crude product which was

purified by column chromatography [eluent: petroleum ether (60-80°C); ethyl acetate (95:5)]

α-Acetoxy - β, γ - unsaturated esters

Compound : (177)



A mobile liquid

Yield 82%

IR spectrum (neat) ν_{max} : 1750, 1740(-O-$COCH_3$, -COOEt) cm^{-1}

^1H NMR spectrum (CCl_4): δ 5.75(1H, br. s, = C<u>H</u>-),

5.35(1H, s, -C<u>H</u>OAc), 4.15(2H, q, -O$C\underline{H}_2CH_3$, J = 7 Hz)

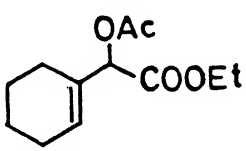
2.3-1.7(9H, m, allylic and other methylenes and -O-C(=O)-CH_3

peak at δ 1.95), 1.15(3H, t, -$OCH_2C\underline{H}_3$)

Mass spectrum (m/z): 212 (M^+), 153 (M^+-59), 43

Anal. Calcd. for: $C_{11}H_{16}O_4$: C, 62.26; H, 7.54; Found: C, 62.5; H, 7.64%

Compound : (178)



A clear liquid

Yield 82%

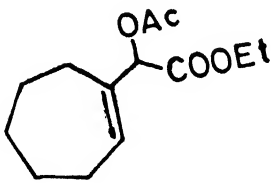
IR spectrum (neat) ν_{max} : 1740(-O-C(=O)-CH_3, -COOEt) cm^{-1}

^1H NMR spectrum (CCl_4): δ 5.78(1H, br. s, = C<u>H</u>-),
5.15(1H, br, s, -C<u>H</u>OAc), 4.25(2H, q, -OC<u>H_2</u>-CH_3),
J = 7 Hz), 2.5-2.2(4H, m, allylic methylenes),
2.2-1.2(7H, m, other methylenes with a singlet
of O-CO-C<u>H_3</u> at δ 2.15 and a triplet of -O-CH_2C<u>H_3</u> at δ 1.15)

Mass spectrum (m/z): 226(M^+), 167 (M^+-59), 43

Anal. Calcd. for: $C_{12}H_{18}O_4$: C, 63.72; H, 7.96; Found: C, 63.5;
H, 7.66%

Compound : (179)



Yield 92%

A clear liquid

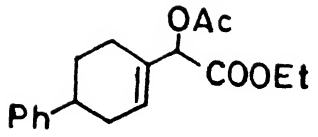
IR spectrum (neat) ν_{max} : 1750-1740 (-COOEt, -OC(=O)-CH_3) cm^{-1}

^1H NMR spectrum (CCl_4): δ 6.08(1H, t, = C<u>H</u>-),
5.15(1H, s, -C<u>H</u>OAc), 4.14(2H, q, -OC<u>H_2</u>CH_3 , J = 7 Hz),
2.35-1.15(13H, m, allylic and other methylenes with a methyl
singlet of -O-CO-C<u>H_3</u> at δ 2.08 and a methyl triplet of
-O-CH_2C<u>H_3</u> at δ 1.3)

Mass spectrum (m/z) 240 (M^+), 181 (M^+-59), 43

Anal. Calcd. for: $C_{13}H_{20}O_4$: C, 65.05; H, 8.3; Found: C, 65.21; H, 8.12%

Compound : (180)



Yield 75%

Viscous liquid

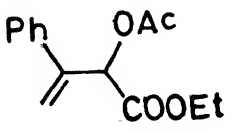
IR spectrum (neat) ν_{max} : 1740- 1720 (-COOEt, -O-C(=O)-CH_3) cm^{-1}

^1H NMR spectrum (CCl_4) : δ 7.15(5H, s, aromatic protons), 5.85(1H, br. s, = C<u>H</u>-), 5.09(1H, s, -C<u>H</u>OAc), 4.03(2H, q, -O-C<u>H</u>$_2$CH$_3$), 2.6-1.06(13H, m, allylic and other methylenes with acetoxy (-O-CO-C<u>H</u>$_3$) singlet at δ2.04 and methyl triplet of -O-CH$_2$C<u>H</u>$_3$ at δ1.24)

Mass spectrum (m/z) : 302(M^+), 243 (M^+-59), 198, 155, 104, 43

Anal. Calcd. for: $C_{18}H_{22}O_4$: C, 71.52; H, 7.28; Found: C, 71.71; H, 7.02%

Compound : (183)



Yield 83%

Viscous liquid

IR spectrum (neat) ν_{max} :1750 - 1740 ($-O-COCH_3$, $-COOCH_2CH_3$) cm^{-1}

^1H NMR spectrum (CCl_4): δ 7.12(5H, m, aromatic protons),

5.54(2H, s, $= CH_2$), 5.30 (1H, s,$-CHOAc$),

3.91(2H, q, $-OCH_2-CH_3$), 2.03(3H, s, $-O-\overset{O}{\overset{\|}{C}}-CH_3$),

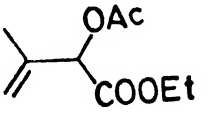
1.03(3H, t, $-OCH_2-CH_3$)

Mass spectrum (m/z): 249 $(M+1)^+$, 207 $[(M^+ +1)-43]$, 189 $(M^+ -59)$

Anal. Calcd. for : $C_{14}H_{16}O_4$: C, 67.74; H, 6.45;

Found: C, 67.66; H, 6.7%

Compound : (186)



Yield 80%

Labile liquid

b.p : 98°C/10 mm (Lit[80] 95°C/10 mm)

IR spectrum (neat) ν_{max} : 1740 - 1730 ($-COOEt$, $-O-CO-CH_3$) cm^{-1}

^1H NMR spectrum (CCl_4): δ 5.35(2H, s, $= CH_2$),

5.03-4.94(1H, m, $-CHOAc$), 4.15(2H, q, $-OCH_2CH_3$),

2.15(3H, s, $-O-CO-CH_3$) 1.78(3H, s, $CH_3-C = CH_2$),

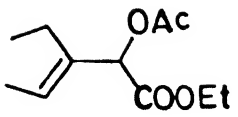
1.36(3H, t, $-OCH_2CH_3$)

Mass spectrum (m/z) :186(M^+), 143 (M^+-43), 127 (M^+-59)

Anal. Calcd. for: $C_9H_{14}O_4$: C, 58.06; H, 7.52; Found: C, 58.5;

H, 7.6%

Compound : (189)



Yield 75%

A freely moving liquid

IR spectrum (neat) ν_{max} : 1745 - 1735 (-COOEt, -O-CO-CH_3) cm^{-1}

^1H NMR spectrum (CCl_4): δ 5.54(1H, q, = C<u>H</u>-),

5.06, 5.03(1H, 2s, -C<u>H</u>OAc), 4.06(2H, q, -O<u>C</u>$H_2$$CH_3$)

2.03(3H, s, -O-CO-CH_3), 1.94(2H, m, >C=C-CH_2-CH_3),

1.7, 1.63(3H, m, two vinylic methyl protons from two

isomer Ca. 1:2), 1.21(3H, t, >C =C-CH_2-CH_3), 0.84(3H, t, -O-CH_2-

Mass spectrum (m/z): 215 $(M+1)^+$, 173 $[(M^+ +1)-42]$, 155 $(M^+ -59)$

Anal. Calcd. for: $C_{11}H_{18}O_4$: C, 61.68; H, 8.41; Found: C, 61.5;

H, 8.6%

I.20 Pig liver acetone powder (PLAP)

This was prepared according to the procedure reported by Ohno et al.[69].

Freshly purchased pig liver (500 g) was homogenised in chilled acetone (2 L) using kitchen juicer. The brown mass obtained after filtration was air dried at room temperature and powdered using grinder. Fibrous material was removed by sieving to furnish 100 g of PLAP as fine powder. This powder can be stored for 2-3 months in refrigerator without any significant

loss of activity.

General procedure

PLAP catalysed hydrolysis[80] of racemic acetates

To 0.5 M, pH 8.0 KH_2PO_4/K_2HPO_4 buffer (20 ml), racemic acetate (500 mg) in ether (10 ml) was added with stirring at 10-15°C. PLAP (600 mg) was added to it and stirring was continued. Progress of the hydrolysis was monitored by TLC. When an appropriate degree of hydrolysis was accomplished, the reaction was quenched with 2(N) HCl (5 ml) so that the pH of the reaction mixture was 6.5. To this, sodium chloride and ethyl acetate were added and the resulting suspension was vigorously stirred for 0.5 hr. Then the enzyme was removed by filtration with suction and the layers were separated. The aqueous layer was extracted with ethyl acetate (3x20 ml) and the combined organic layer was washed with brine (10 ml), dried over anhydrous Na_2SO_4 and concentrated. The crude liquid obtained was purified by column chromatography (eluent: 6% ethyl acetate in pet ether [60-80°C]) to get optically active alcohol and enantiomerically enriched unhydrolysed acetate.

PLAP catalysed hydrolysis of (±) Ethyl-2-acetoxy-2-(1-cyclohexenyl) acetate (± 178)

Hydrolysis of racemic (**178**) (500 mg 2.21 mmol) with PLAP (600 mg) afforded alcohol (+) **119b** and unhydrolyzed acetate (-) **178**.

Reaction time : 72 hr.

Yield of (+) alcohol : 165 mg (81%)

$[\alpha]_D^{25}$: (+) 35.563 (Cl, $CHCl_3$)

e.e : 90%

Yield of recovered acetate : 285 mg

$[\alpha]_D^{25}$: (-) 28.473 (Cl, $CHCl_3$)

e.e : 54%

Both alcohol (+) **119b** and acetate (-) **178** have IR, ^1H NMR data identical with that of the corresponding racemic compound.

PLAP-Catalyzed hydrolysis of (±) Ethyl-2-acetoxy-2-(1-cyclopentenyl) acetate (177)

Hydrolysis of racemic (±) **177** (400 mg, 1.88 mmol) with PLAP (480 mg) afforded alcohol (+) **119a** and unhydrolysed acetate (-) **177**.

Reaction time: 64 hr

Yield of (+) alcohol: 75 mg (47%)

$[\alpha]_D^{25}$: (+) 29.016 (Cl, $CHCl_3$)

e.e : 82%

Yield of (-) acetate: 250 mg

$[\alpha]_D^{25}$: (-) 28.475 (Cl, $CHCl_3$)

e.e : 44%

Both alcohol (+) **119a** and acetate (-) **177** have IR, ^1H NMR data identical with that of the corresponding racemic compound.

PLAP-Catalysed hydrolysis of (±) Ethyl-2-acetoxy-2-(1-cycloheptenyl) acetate (179)

Hydrolysis of racemic (±)**179** (480 mg, 2 mmol) with PLAP (576 mg) afforded alcohol (+) **119c** and unhydrolysed acetate (-) **179**.

Reaction time : 75 hr

Yield of (+) alcohol : 70 mg (35%)

$[\alpha]_D^{25}$: (+) 108.14 [Cl, $CHCl_3$]

e.e : 80%

Yield of (-) acetate : 250 mg

$[\alpha]_D^{25}$: (-) 82.56 [Cl, $CHCl_3$)

e.e : 34%

Both alcohol (+) **119c** and acetate (-) **179** have IR, ^1H NMR data identical with that of the corresponding racemic compound.

PLAP-catalysed hydrolysis of (±) Ethyl-2-acetoxy-2 (4 phenyl-1-cyclohexenyl) acetate (180)

Hydrolysis of (±) **180** (800 mg, 2.64 mmol) with PLAP (960 mg) afforded alcohol (-) **119e** and unhydrolysed acetate (+) **180**.

Reaction time: 70 hr

Yield of (-) alcohol: 100 mg (29%)

$[\alpha]_D^{25}$: (-) 7.8554 [Cl, $CHCl_3$]

e.e : 69%

Yield of (+) acetate: 543 mg

$[\alpha]_D^{25}$: (+) 9.7419

e.e : 53%

Both alcohol (-) **119e** and acetate (+) **180** have IR, ^1H NMR data identical with that of the corresponding racemic compound.

PLAP-catalysed hydrolysis of (±) Ethyl-2-acetoxy-3-phenyl- but-3-enoate (183)

Hydrolysis of racemic (±) **183** (400 mg, 1.61 mmol) with PLAP (480 mg) afforded alcohol (+) **182** and unhydrolysed acetate (-) **183**.

Reaction time : 74 hr

Yield of (+) alcohol: 60 mg (36%)

$[\alpha]_D^{25}$: (+) 6.69 [Cl, $CHCl_3$]

e.e : 65%

Yield of (-) recovered acetate: 160 mg

$[\alpha]_D^{25}$: (-) 8.79 [Cl, $CHCl_3$]

e.e : 20%

Both alcohol (+) **182** and acetate (-) **183** have IR, ^1H NMR data identical with that of the corresponding racemic compound.

PLAP catalysed hydrolysis of (±) Ethyl-2-acetoxy-3 methyl-but-3 enoate (186)

Hydrolysis of (±) **186** (462 mg, 2.48 mmol) with PLAP (555 mg) afforded only unhydrolysed acetate (-) **186**.

Reaction time : 70 hr

Yield of (-) acetate : 187 mg

$[\alpha]_D^{25}$: (-) 15.033 (Cl, $CHCl_3$)

e.e : 40%

The acetate (-) **186** has IR, ^1H NMR data identical with that of the corresponding racemic compound.

PLAP catalysed hydrolysis of (±) Ethyl-2 acetoxy-3 ethyl- Pent-3-enoate (189)

Hydrolysis of (±) **189** (560 mg, 2.61 mmol) by PLAP (675 mg)

afforded unhydrolysed acetate (-) **189**.

Reaction time : 85 hr

Yield of (-) acetate : 300 mg

$[\alpha]_D^{25}$: (-) 20.890 (C1, $CHCl_3$)

e.e : 29%

The acetate (-) **189** has IR, ^1H NMR data identical with that of the corresponding racemic compound.

I.21 General procedure for the determination of enantiomeric purity via Mosher's ester

Mosher's ester of (±) alcohol:

To a solution of (±) alcohol (0.09 mmol) and pyridine (0.05 ml), DMAP (5 mg) was added and stirred for 15 min. To this, a solution of (+) α- methoxy- α- (trifluoromethyl) phenyl acetyl chloride (MTPACL) (0.1 mmol) in dichloromethane (1 ml) was added and the mixture was stirred for 24 hr. It was then poured into cold 3N HCl (5 ml) and extracted with ether (3x10 ml). The ether layer was washed with saturated $NaHCO_3$, water (2x5 ml), brine (5 ml) and dried over anhydrous Na_2SO_4. Removal of solvent followed by quick purification on column (SiO_2) [(7% ethyl acetate in (60-80°C) petroleum ether] of the residue afforded pure Mosher's ester.

Mosher's ester of (+) alcohol

Mosher's ester of (+) alcohol was prepared from (+) MTPACl and the corresponding alcohol following the same procedure as described for Mosher's ester of (±) alcohol.

The spectral properties of the Mosher's ester prepared by this procedure are the following:

Mosher's ester of (±) (119b)

A viscous liquid

^{1}H NMR ($CDCl_3$) : δ 7.7-7.2(5H, m, aromatic protons), 5.9-5.8(1H, 2s, = CH-), 5.35 and 5.33 (1H, 2s -$CHCO_2Et$), 4.2(2H, m, -$COOCH_2CH_3$), 3.62 and 3.52 (3H, 2s, Ca. 1:1), -C(Ph)OCH_3)
CF_3
1.8-1.0(9H, m, allylic and other methylenes and methyl triplet of -OCH_2CH_3)

Two distinct singlets of almost equal intigration appeared at δ3.62 and δ3.52 due to -OMe protons indicating that the compound is a 50.50 mixture of two diastereomers.

Mosher's ester of (+) (119a)

A clear liquid

^{1}H NMR ($CDCl_3$) : The ^{1}H NMR spectrum of this compound contains two singlet at δ3.6583 and δ3.5639 with a intensity ratio 3.388: 33.706 establishing the enantiomeric purity of (+) **119a** is 82%

Mosher's ester of (+) (119b)

A viscous liquid

^{1}H NMR ($CDCl_3$): The ^{1}H NMR spectrum of this compound contains two singlet at δ 3.6375 and at δ 3.5380 with a intensity ratio 5 : 95 establishing the enantiomeric purity of (+) **119b** is 90%

Mosher's ester of (+)(119c)

A viscous liquid

^{1}H NMR ($CDCl_3$) : The ^{1}H NMR spectrum of this compound contains two singlet at δ 3.6583 and at δ 3.5639 with a intensity ratio 1.7: 15.9 establishing the enantiomeric purity 80%.

Mosher's ester of (+)(119e)

A thick liquid

^{1}H NMR ($CDCl_3$) : The ^{1}H NMR spectrum of this compound contains two singlet at δ 3.59 and at δ 3.42 with a intensity ratio 5.5 : 1 establishing the enantiomeric purity 69%.

Mosher's ester of (+)(182)

A thick liquid

^{1}H NMR ($CDCl_3$) : The ^{1}H NMR spectrum of this compound contains two singlets at δ 3.685 and at δ 3.615 with a intensity ratio 9.5: 2 indicating the enantiomeric purity 65%.

I.22 Determination of enantiomeric excess of (±) and (-) acetates

The ^{1}H NMR (400 MHz) spectrum of Acetates (5 mg) were recorded in the presence of (+) $Eu(hfc)_3$ (20 mg).

The characteristics of spectra are give below.

Compound (±) (178)

The ^{1}H NMR spectrum of (±) **178** (5 mg) having two singlets at δ 2.25 and δ 2.18 due to methyl protons of ($-O-CO-CH_3$) with an intensity ratio 1:1 clearly shows that the presence

of two enantiomers in the equal amount.

Compound (-)(177)

The ^1H NMR spectrum of (-) **177** (5 mg) having two distinct singlets at δ 2.20 and δ 2.17 due to methyl protons of $-OCO-CH_3$ with an intensity ratio of 72 : 28 shows that the optical purity of the chiral acetate is of 44%.

Compound (-) (178)

The ^1H NMR spectrum of (-) **178** (5 mg) having two singlets at δ 2.25 and δ 2.1 due to methyl protons of ($-OCO-CH_3$) with an intensity ratio of 3.37: 1 shows that the optical purity of the chiral compound is of 54%.

Compound (-)(179)

The ^1H NMR spectrum of (-) **179** (5 mg) having two distincts singlets at δ 2.28 and δ 2.13 due to methyl protons of ($-O-CO-CH_3$) with an intensity ratio of 2.03:1 shows that the optical purity of the chiral acetate is of 34%.

Compound (+)(180)

The ^1H NMR spectrum of (+) **180** with two singlets due to the methyl protons of ($-O-CO-CH_3$) at δ 2.5 and δ 2.42 having an intensity ratio of 6.5: 2 clearly shows that the optical purity of the chiral acetate is of 53%.

Compound (-)(183)

The ^1H NMR spectrum of (-) **183** with two singlets due to the methyl protons of ($-O-CO-CH_3$) at δ 2.44 and δ 2.46 having an

intensity ratio of 40 : 60 indicates its enantiomeric purity 20%.

Compound (-)(186)

The ^1H NMR spectrum of (-) **186** with two singlets due to the methyl protons of (-O-CO-CH_3) at δ2.502 and δ2.506 having an intensity ratio of 70 : 30 indicates its enantiomeric purity 40%.

Compound (-)(189)

The ^1H NMR spectrum of (-) **189** with two singlets due to the methyl protons of (-O-CO-CH_3) at δ2.49 and δ2.4 having an intensity ratio of 1: 1.83 indicates its enantiomeric purity 29%.

I.23 Synthesis of chiral vinyl epoxide

I.23.1 $LiAlH_4$ reduction of (+)(119b)

Procedure: 1 mmol of (+) **119b** was reduced with $LiAlH_4$ following the same procedure as described in section I.7.

Yield of the diol (+) **150b** : 50%

Other physical properties of the diol (+) **150b** are same as described in section I.13 for (-) **150b**.

I.23.2 Epoxidation of (+)(150b)

Procedure : 1 mmol chiral diol (+) **150b** was converted to chiral vinyl epoxide (+) **152b** following the same procedure as described in section I.8.

Yield : 72%

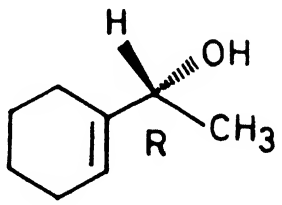
$[\alpha]^{25}_{D}$: (+) 3.226 (Cl, $CHCl_3$)

Other physical properties are same as given in section I.9 for (±) **122b**.

I.23.3 Determination of absolute configuration of chiral vinyl epoxide (+)(152b)

Procedure: 0.5 mmol of chiral vinyl epoxide (+) **152b** was reduced with $LiAlH_4$ following the same procedure as described in section I.16.

Compound [(+) 153]



Yield : 65%

A mobile liquid

$[\alpha]^{25}_{D}$: (+) 12.15 (Cl, $CHCl_3$)

$[\alpha]^{25}_{D}$: (-) 9.8 (Cl, $CHCl_3$) Lit[63]

e.e : 90%

IR and ^1H NMR are same as written in section I.16

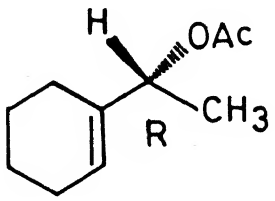
So the absolute configuration of (+) **153** is R

I.23.4 Acetylation of (+) 153:(154)

Yield : 85%

$[\alpha]^{25}_{D}$: 27.433 (Cl, $CHCl_3$)

e.e : 90% (by using shift reagent)



Spectroscopic details are same as described in Section I.16.

I.24 PLAP catalysed hydrolysis of 1-(Cyclohex-1-ene)-1,2-diacetoxy ethane (121b)

452 mg (2 mmol) of **121b** was hydrolysed with 550 mg PLAP following the same procedure[80] as detailed in Section I.20.

Four chiral compounds were isolated whose physical properties are given below.

1-(Cyclohex-1-ene)-1,2-diacetoxy ethane: (-) (121b)

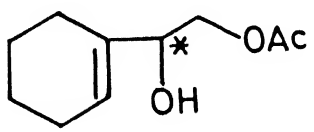
A colourless viscous liquid

Yield : 67%

$[\alpha]^{25}_{D}$: (-) 8.2562

^{1}H NMR , IR and Mass spectrum are same as is given in Section I.8.

1-(Cyclohex-1-ene)-2-acetoxy-ethanol: (-) (190)



An oily liquid

Yield : 12%

IR spectrum (neat) ν_{max}: (3445, 1730) cm^{-1} (-OH,-COOEt)

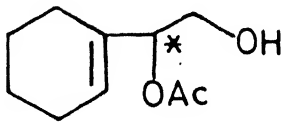
^{1}H NMR spectrum (CCl_4): δ 5.55(1H, br.s, =CH-), 3.9(3H, m,-CHOH-CH_2OAc) 2.7(1H, br.s, -CH-OH), 2.1-1.3(11H, m, allylic and other methylenes with the methyl singlet of the -O-CO-CH_3 group

centred at δ1.95.

$[\alpha]^{25}_{D}$: (-) 13.95 (Cl, $CHCl_3$)

Mass spectrum (m/z): 186 (M+2), 184 (M^+), 168 (M+2-H_2O)

2-(Cyclohex-1-ene)-2-acetoxy-1-ethanol: (-) (191)



An oily liquid

Yield : 7%

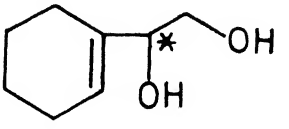
IR spectrum (neat) ν_{max}: (3440, 1725) (-OH,-COOEt) cm^{-1}

^1H NMR spectrum (CCl_4): δ 5.6(1H, br.s, = CH-), 5(1H, t, -CHOAc-CH_2OH), 3.5(2H, d, -CHOAc-CH_2OH), 2.15- 1.45(11H, m, allylic and other methylenes with an methyl peak of -OCO-CH_3 centred at δ 2.06

$[\alpha]^{25}_{D}$: (-) 25.952 (C1, $CHCl_3$)

Mass spectrum (m/z): 184 (M^+), 167 (M+1-H_2O), 125 (M^+-O-C(=O)-CH_3)

1-(Cyclohex-1-ene)-1-(β-hydroxy-ethanol: [(+) 192]



A viscous liquid

Yield : 7.04%

$[\alpha]^{25}_{D}$: (+) 25.939 (C1, $CHCl_3$)

IR, ^1H NMR and Mass spectrum are same as described in Section I.7

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CHAPTER II

SYNTHESIS AND REACTIONS OF SOME USEFUL SULFUR CONTAINING SYNTHONS

II.1 INTRODUCTION

Although organosulfur chemistry can be traced back to the very beginning of organic chemistry, the versatility of sulfur continues to lead to fascinating new chemistry. The existence of so many valence states of sulfur has generated selective and novel ways to effect oxidation, and carbon-carbon bond formation. The ability of sulfur to stabilise positive or negative charges on adjacent carbon has been especially important in the development of new ways to form carbon-carbon bonds. Sulfides, sulfoxides and sulfones all play an important role in those above mentioned reactions. Among these allyl and vinyl sulfides are specially noteworthy as they are having an added functional group, the olefinic bond. For these reasons they have proved to be extremely useful synthons and these properties continue to evolve new reactions and sequences which facilitate the design of the total synthesis of complex organic molecules. A brief literature survey dealing with the utility of such intermediates in organic synthesis has been discussed in the following few pages.

Solvolysis of vinyl sulphides **1** yields a hemiacetal or O, S-acetal **3** formed through the carbocation **2**. The desired final products are acetals **5** (formed especially instead of free aldehydes in alcoholic solvents) or carbonyl compounds **4** (water) (Fig. 1).

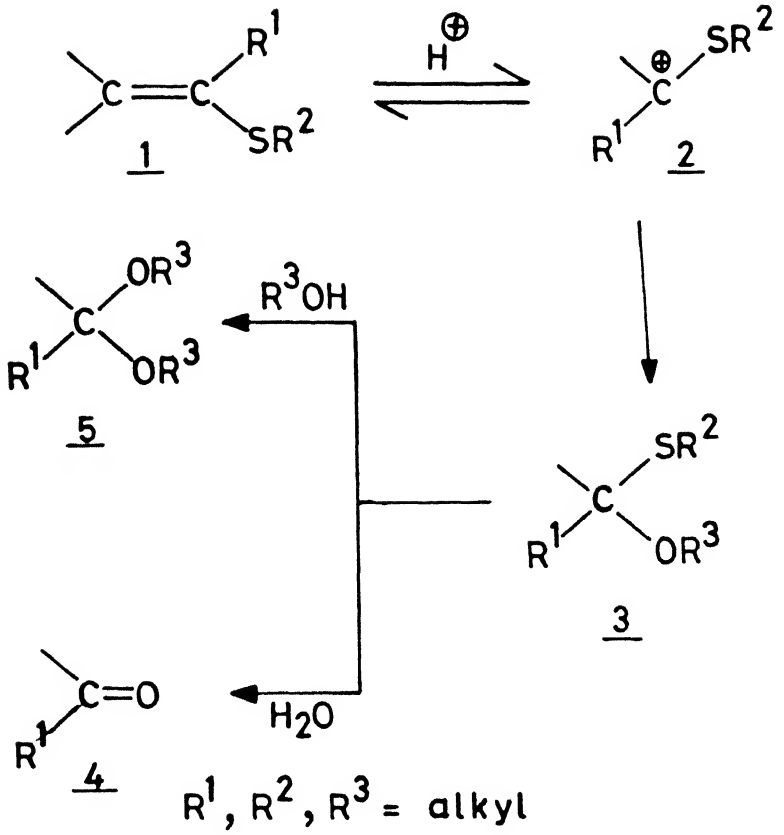


Figure 1

But in the above mentioned hydrolysis the equilibrium lies far to the left. Therefore only irreversible removal of the solvolysis products can push it to the right[1]. This problem has been circumvented by the use of transition metal salts such as $HgCl_2$[2], HgO[3], Cu (II) salt[4] and titanium (IV) chloride[5] (Fig. 2).

α- Thioorganometallics have proved to be extremely useful reagents and they have been used extensively in synthesis over the past 20 years. Upon reaction with compounds bearing an electrophilic carbon atom, they allow the efficient formation of a new carbon-carbon bond to which the heteroatomic moiety is directly linked. The large variety of reactions possible through use of organosulfur reagents with subsequent selective removal of the heteroatomic moiety permits the synthesis of a large variety compounds.

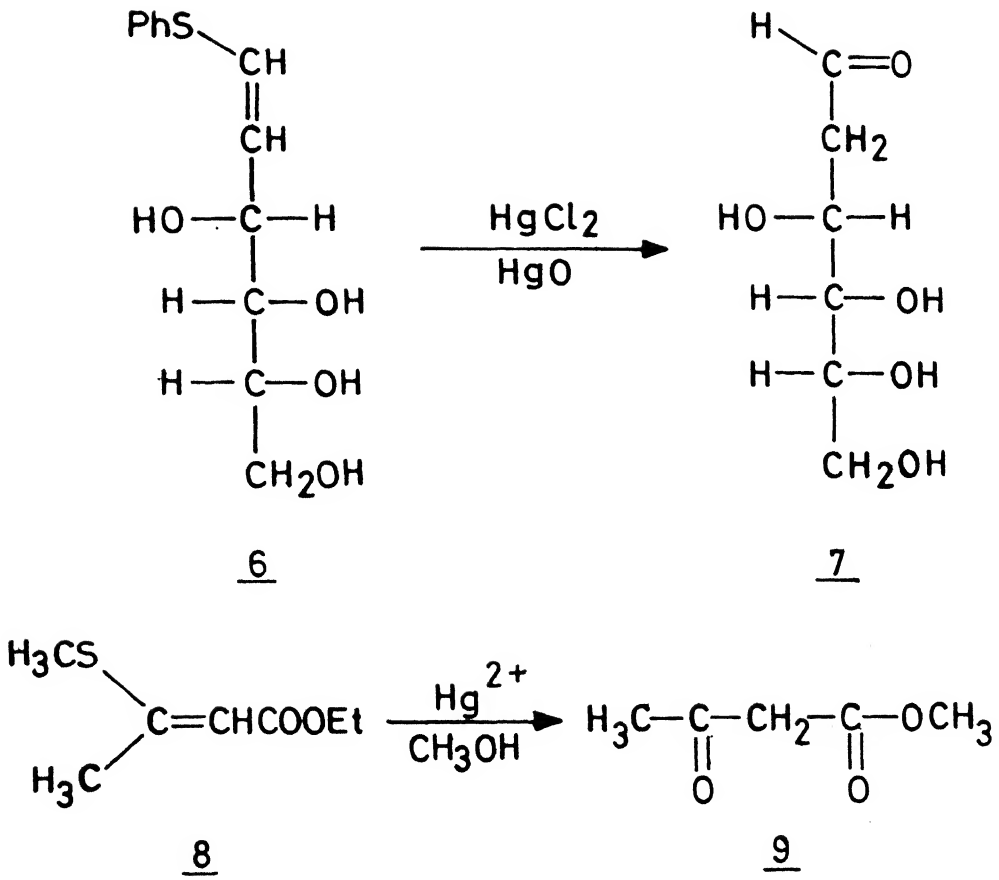

PhS
CH
CH
HO—C—H
H—C—OH
H—C—OH
CH2OH
HgCl2
HgO
H
C=O
CH2
HO—C—H
H—C—OH
H—C—OH
CH2OH
6
7
H3CS
C=CHCOOEt
H3C
Hg2+
CH3OH
H3C—C—CH2—C—OCH3
O
O
8
9

Figure 2

Generally butyllithiums in THF have been used successfully for the metallation of vinyl sulfides[6] and the lithiated compounds react with the electrophiles E^+ to form various products. The synthetic utility of metallated vinyl sulphides is amply available in the literature; a few of which are discussed here. α - Lithiovinyl sulphide is important ketone equivalent that gives (after alkylation and hydrolysis) ketone with alkyl halide **12**, acyloin with aldehyde **14** and α,β - unsaturated ketone with epoxides **16**, diketone with α,ω - dihalide **18**[7] (Fig. 3).

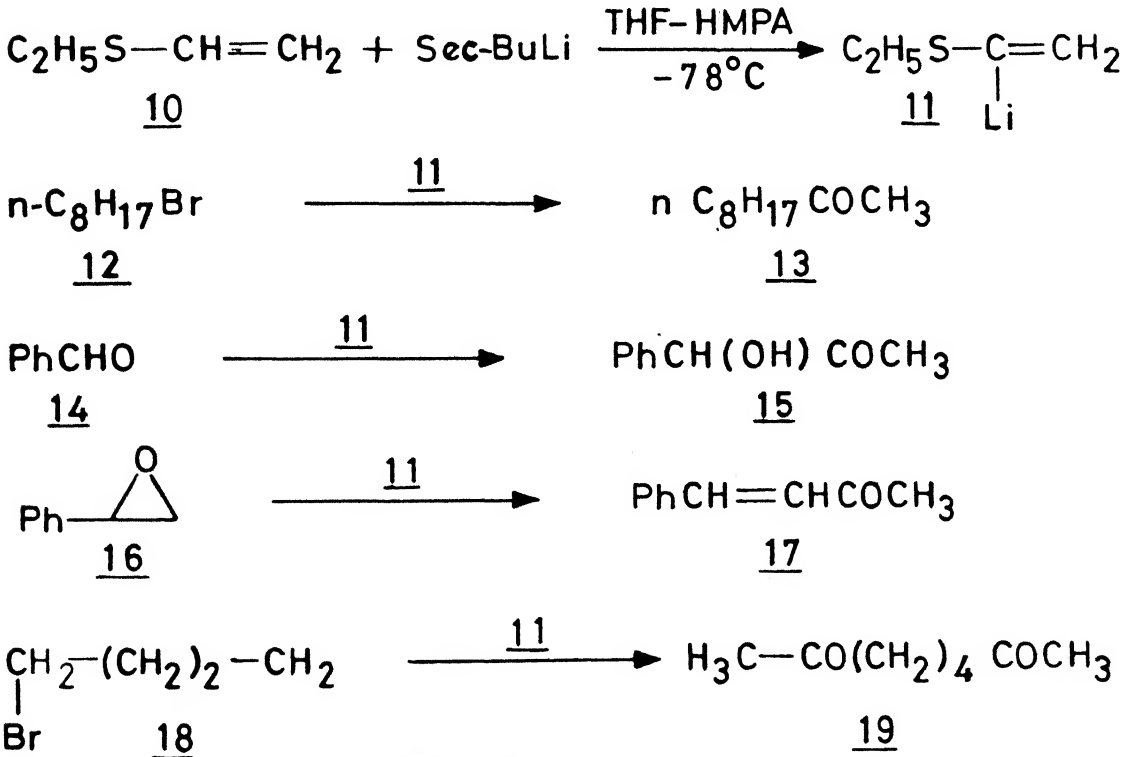


Figure 3

These metallation reactions have some difficulties which are as follows.

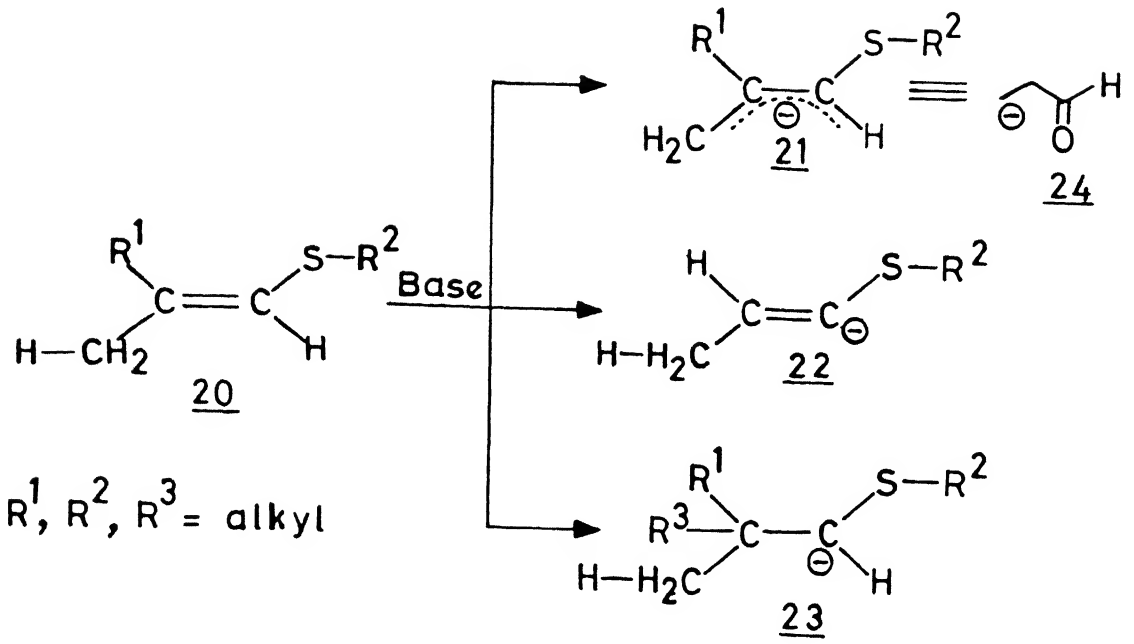


Figure 4

The deprotonation sequence **20** ---> **22** is not very clear-cut as allylic protons, if present in **20**, can be abstracted instead leading to the allylic anions, which can react in the α or γ position (synthetic equivalent **24**) of the heterosubstituents. Furthermore, the proton abstracting reagent may add to the thioenolether's double bond to give **23**. But the different modes of reactions of **20** can be controlled to a large extent by varying the conditions. Thus reaction with sec-butyllithium leads to abstraction of an α - proton from thioenol ethers **20** ---> **22** whereas treatment with lithium diisopropylamide tends to deprotonate an allylic carbon **20** ---> **21** (Fig. 4).

1,3-Dienyl sulphide **25** has been selectively alkylated at the α- vinylic site by use of a strong metallating base such as Bu^n Li- Bu^tOK[8] (Fig. 5).

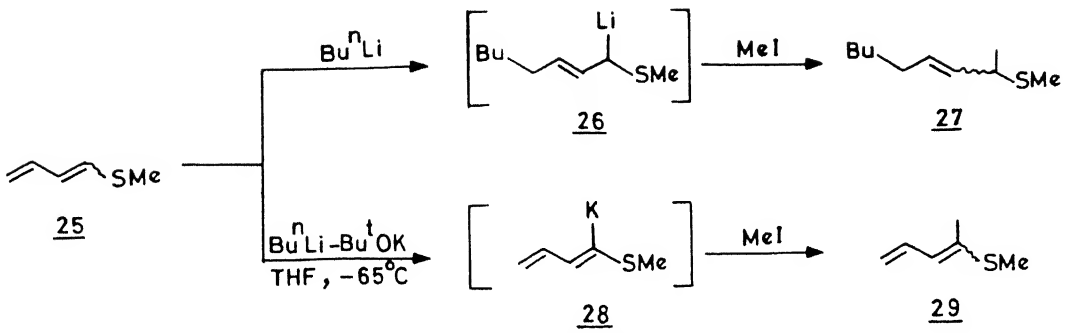
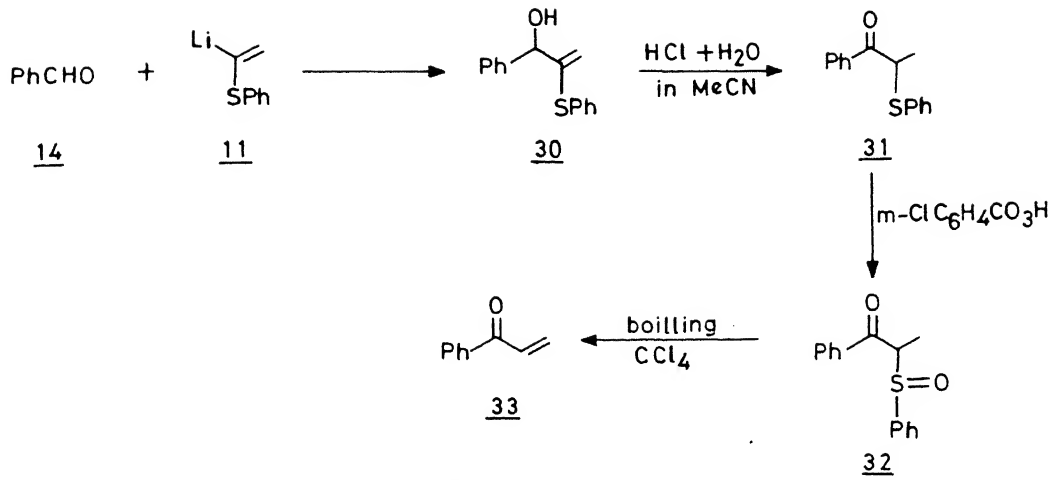


Figure 5

Another example in which utility of α- thiovinyl lithium compounds is demonstrated involves conversion of benzaldehyde into α, β unsaturated ketones[9]. This is based on acid catalysed isomerisation of 1-(phenylthio)vinyl lithium-aldehyde adduct **30** followed by oxidative desulphurisation (Fig. 6).

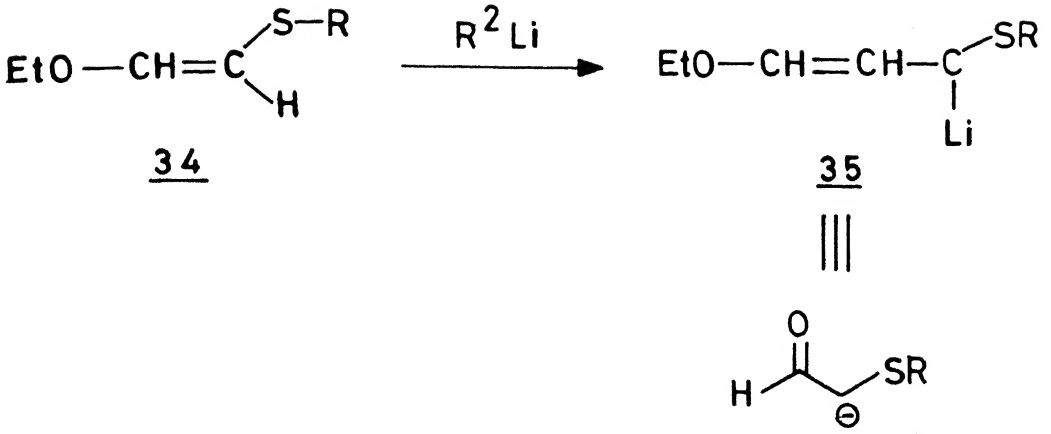


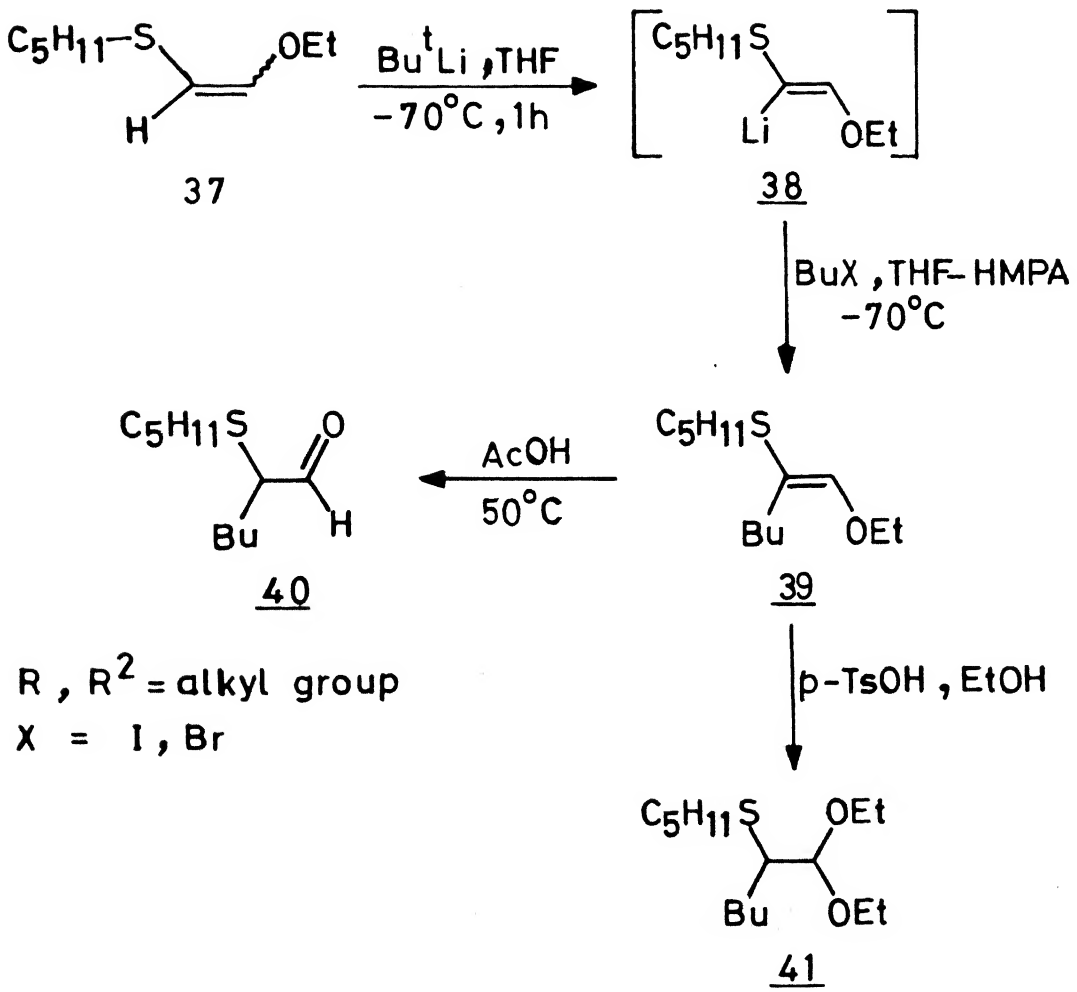
14 11 30 31 32 33

Figure 6

Compounds of the type **34** are useful synthetic equivalents[10] of the enolate of α- thiolated acetaldehydes **40**. Synthetic usefulness of these types of compounds is shown with an example in Fig. 7.

1-Metallovinyl sulphides **42** can be methylated with methyl iodide also[11] and the corresponding ketone is obtained after hydrolysis Fig. 8.





R, R^2 = alkyl group

X = I, Br

Figure 7

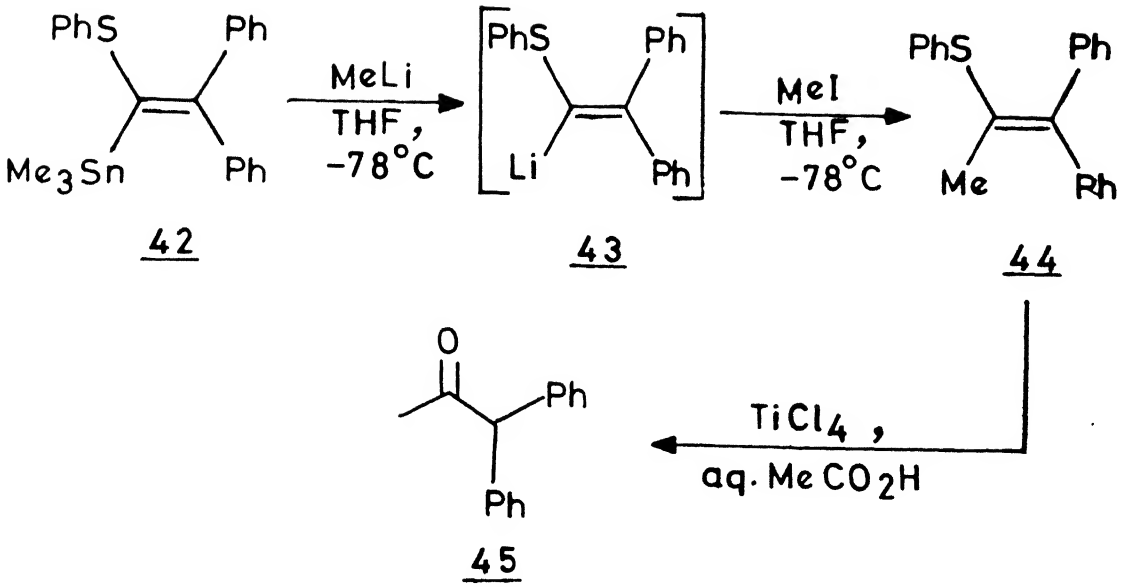


Figure 8

2-Methoxy-3- phenylthio-1, 3-butadiene is a useful diene **46**, containing a vinyl sulfide moiety. This has been used in the normal orientations of Diels-Alder annelations that will compliment the regiochemistry obtainable with 2 oxygenated dienes. Its use permits a masked β-ketosulfide to be introduced into ring system[12] (Fig. 9).

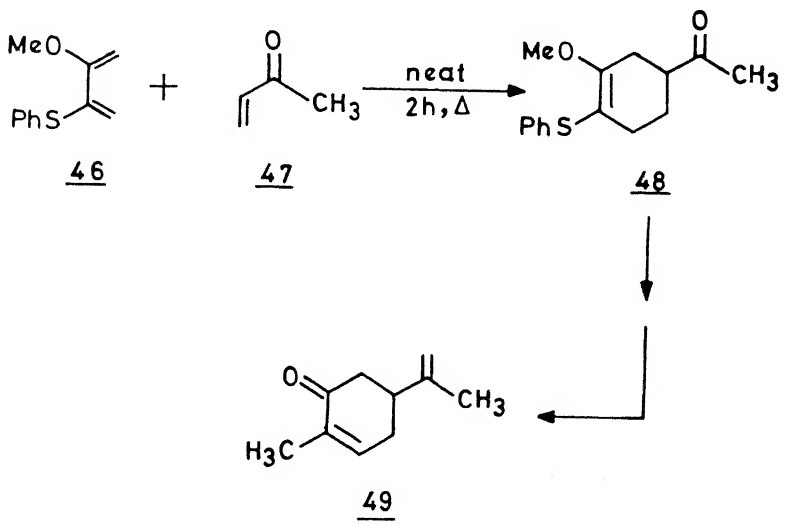


Figure 9

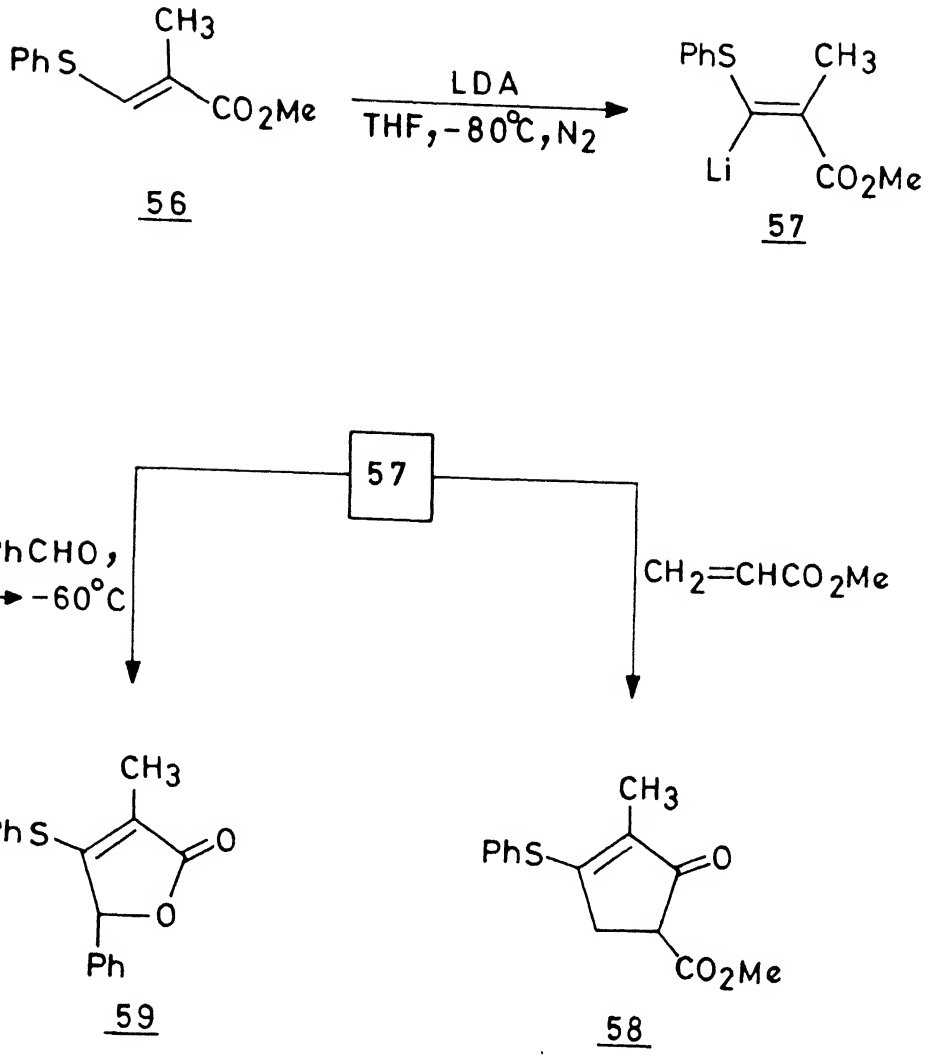


Figure 11

Michael addition of methyl 3-lithio-2- methyl-3-phenylthio-2-propeonate **57** to the acrylate gives the functionalised cyclopentenone **58** while addition to aldehydes is followed similarly by cyclisation to furan-2-ones[14] **59** (Fig. 11).

Thio substituted allylic anions **60** which react with electrophiles in the γ-position, are potentially useful reagents because the products **61** of this coupling are derivatives of aldehydes or ketones. But the problem arises in directing the formation of **61** as a major product as there is an equal

probability of formation of **63** (Fig. 12). So far there are no foolproof rules about how to control this α / γ ambiguity completely. However by varying different conditions α or γ selectivity could be achieved.

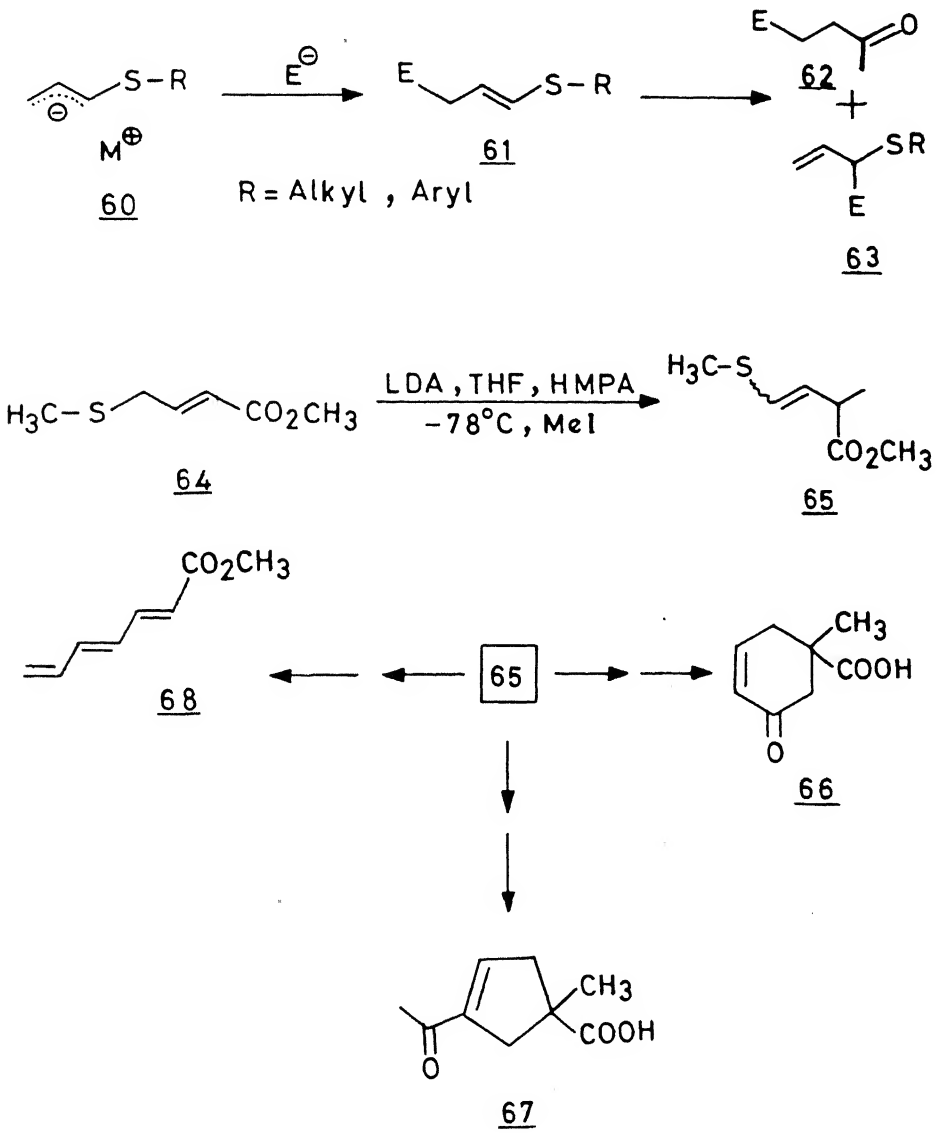
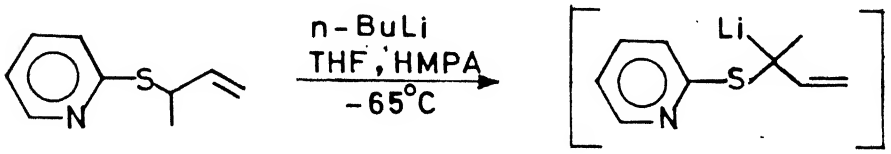
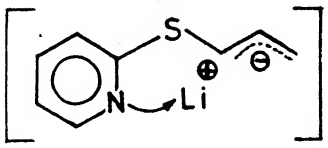


Figure 12

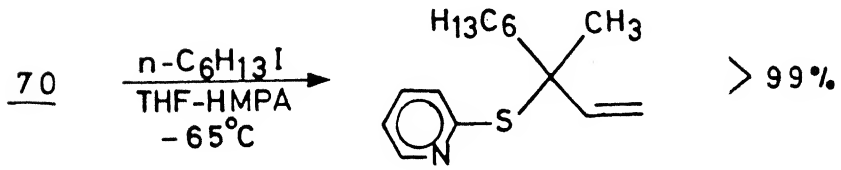
Kende et al[15] were successful to get 100% γ substituted adduct **65** from methyl γ - methyl thiocrotonate **64** which has been shown to be a useful synthon for the synthesis of cyclohexenone **66**, acylcyclopentenone **67**, and a triene carboxylic acid **68** derivative (Fig. 12). Lithium chelation[16] with nitrogen in the case of thioallyllithium **70** at the α site exhibits a dramatic selectivity for α-alkylations (Fig. 13).



69 70(a)



70(b)



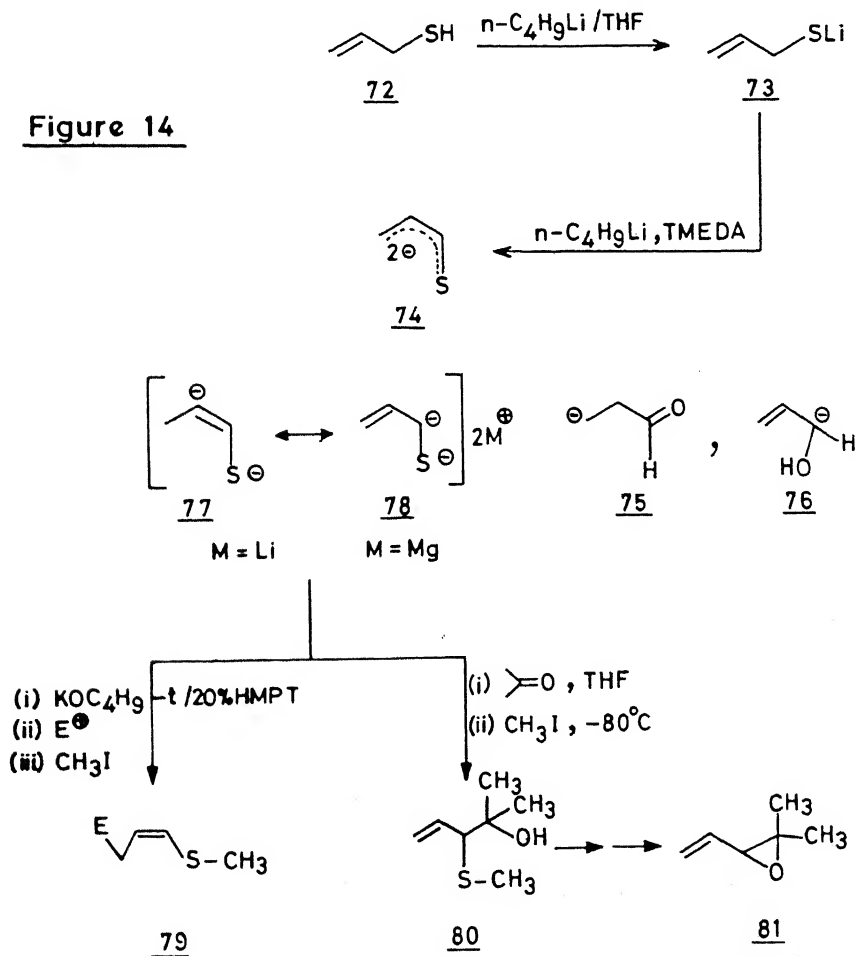
71

Figure 13

Further work has resulted in three more possibilities through which the inherent α- reactivity of metallated allyl sulfides has been converted to selective γ- reactivity: (a) a thioallylic dianion is used (b) the α and γ positions are made equivalent (c) a 1, 3- shift is carried out after the α- reaction.

(a) Thus treatment of allyl mercaptan with two equivalents of butyllithium gives a dianion **74**, the lithioderivative of which reacts with electrophiles in the γ position[17], while the magnesium[18] derivative combines with carbonyl compounds exclusively at the carbon atom next to sulfur and the product gives oxirane **81** on further reaction (Fig. 14).

Figure 14



Transformation of the primary products to sulfur free compounds shows that the dianion can be synthetically applied as one of the building blocks **75** and **76** (Fig. 14).

(b) If the two ends of the allylic anion are both heterosubstituted, it does not make any difference which end reacts. 1-Metallo-1, 3 di(thio)propene **82** plays the role of β-metallo-α, β-unsaturated aldehyde (-CH=C-CHO) (Fig. 15), has proved particularly useful for the synthesis of δ-alkoxy-α, β-unsaturated aldehydes[19] They have been used in[19,20]. the neat synthesis of Prostaglandin $F_{2\alpha}$ **91** from a functionalized oxidocyclopentene derivative (Fig. 15).

(c) Appropriate α adducts can be rearranged to the γ adducts by sigmatropic shifts.

A special advantage is the fact that conversion of the alkylated allyl sulphide into the corresponding sulphoxide, followed by rearrangement, places an oxygen function on the carbon atom of the original allyl grouping. Nuciferol is synthesised[21] by using this rearrangement (Fig. 16).

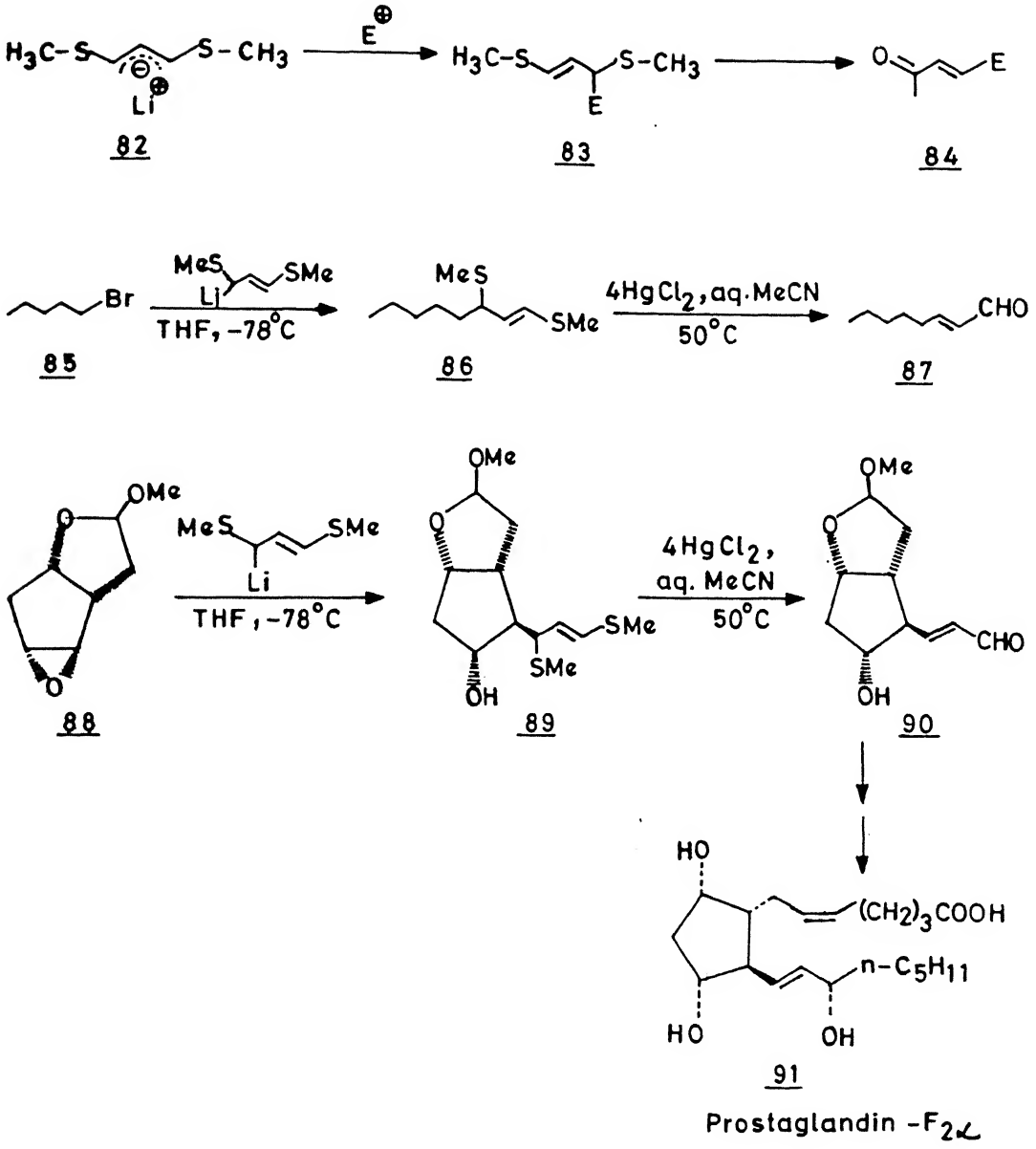

H3C-S
S-CH3
Li
E
82
83
84
Br
MeS
SMe
Li
THF, -78°C
85
86
4HgCl2, aq. MeCN
50°C
87
CHO
OMe
O
88
89
90
OH
HO
(CH2)3COOH
n-C5H11
91
Prostaglandin -F2α

Figure 15

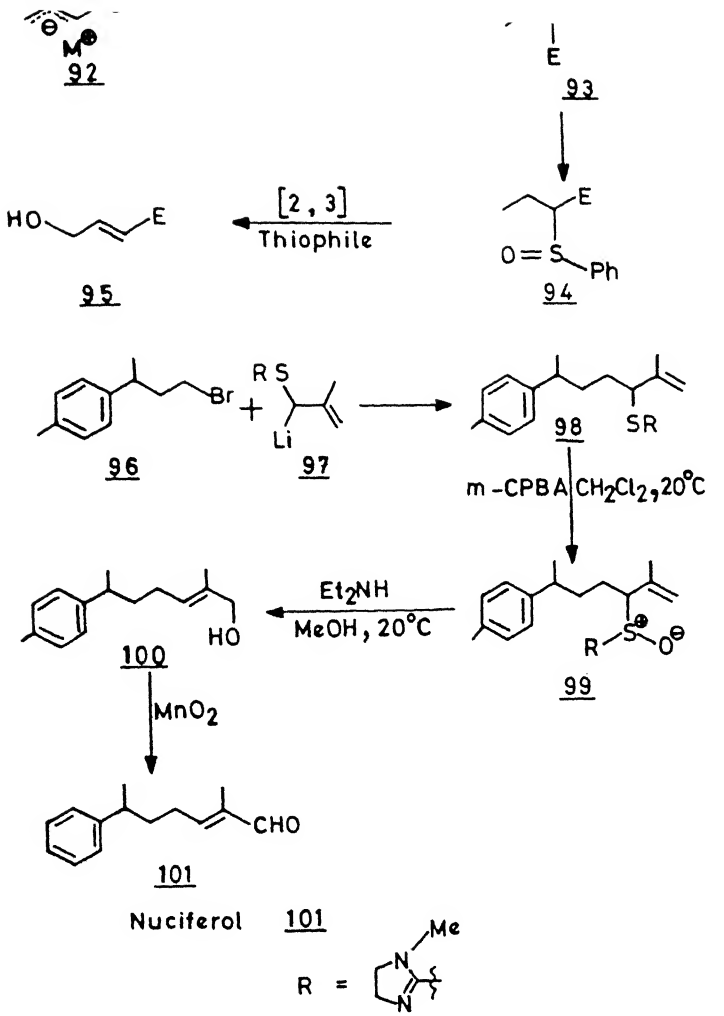


Figure 16

The delocalised anion **60** is representative of the crucial intermediate in many applications of allyl sulphides in synthesis. Reactions between α-thio allyl lithiums and alkyl halides which usually proceeds predominantly via α - α' (head-to-head) coupling have proved to be valuable in synthesis[22,23]. They have been used successfully for example in the synthesis of 1, 5- dienes such as squalene[22] **106**, R - (+) - 10, 11 - epoxyfarnesol[23]. Hirai et al have synthesised squalene[22] from 2-alkenenylthiothiazoline lithium derivative **103** (Fig. 17).

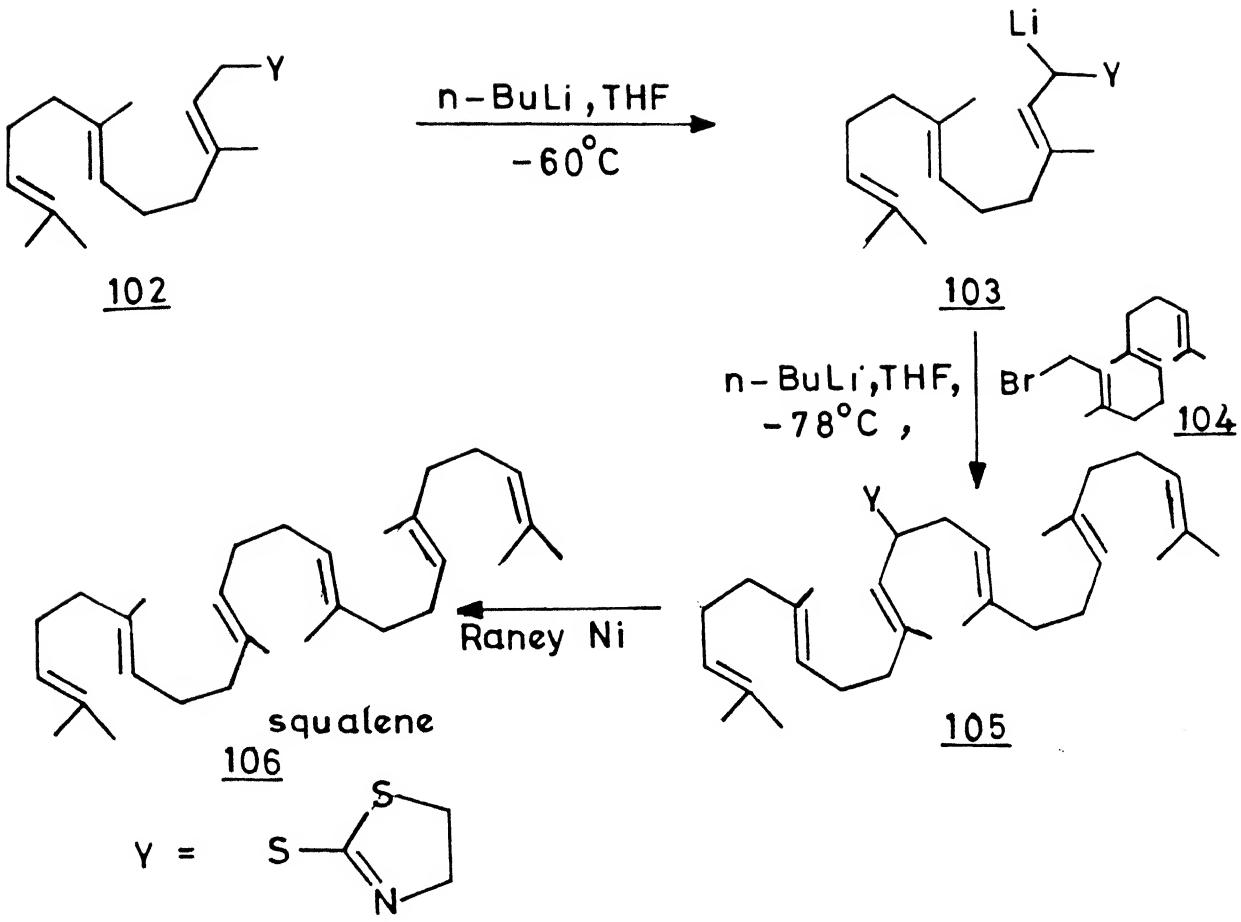


Figure 17

Allylation of alkylthioallyl copper compounds, generated in ether from alkylthioallyllithium and CuI at -78°C affords exclusively[24] $\gamma - \gamma'$ (tail to tail) coupled products, whereas alkylthio allylic aluminium[25] complexes, readily available from reaction of alkylthioallyllithium compounds with trialkyl aluminium, undergo regiocontrolled $\alpha - \alpha'$ (head to tail) coupling with allylic halides[26] **112** (Fig. 18).

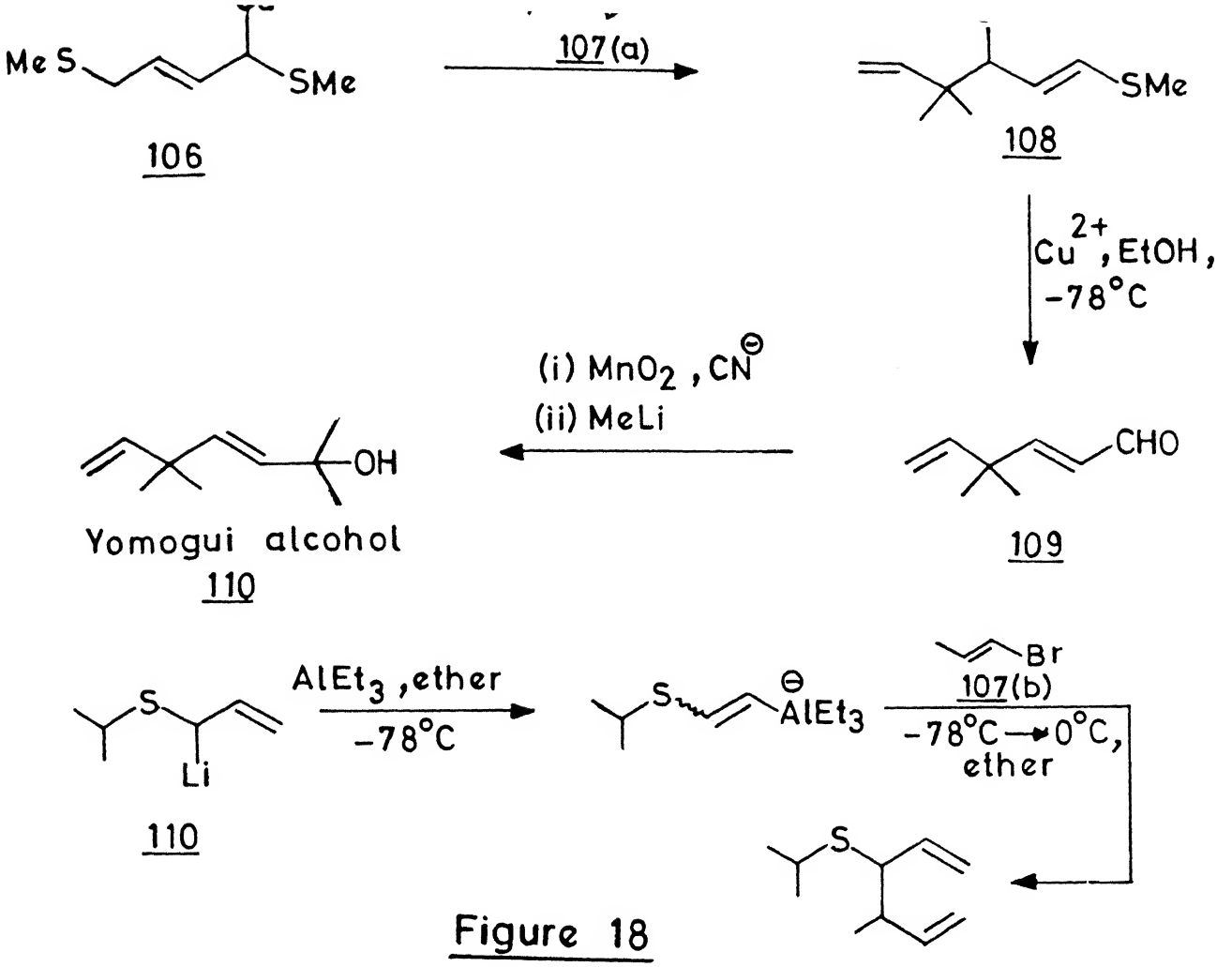


Figure 18

Reactions between α- thioallyllithiums and epoxides have been used in a large number of important syntheses. Most of these reactions involve intramolecular reactions and the synthesis of macrocyclic terpenoids from trisubstituted epoxides[27] (Fig. 19).

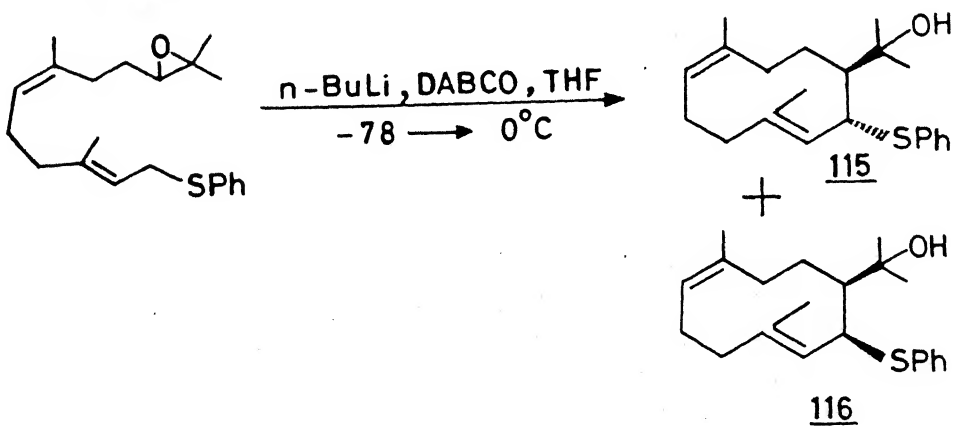


Figure 19

Metalloallyl vinyl sulfides[28] and their ethoxy[29] analogs have been selectively alkylated, benzylated and allylated at their α - site and then the resulting compounds have been thermally rearranged [Claisen-Cope rearrangement: (3,3) sigmatropic shift] to γ, δ -unsaturated aldehydes or γ - oxo aldehydes on heating in aqueous DME. Yamamoto[28] et al have synthesised cis-jasmone **125** (Fig. 20) using this 2-ethoxyallyl vinyl sulfide.

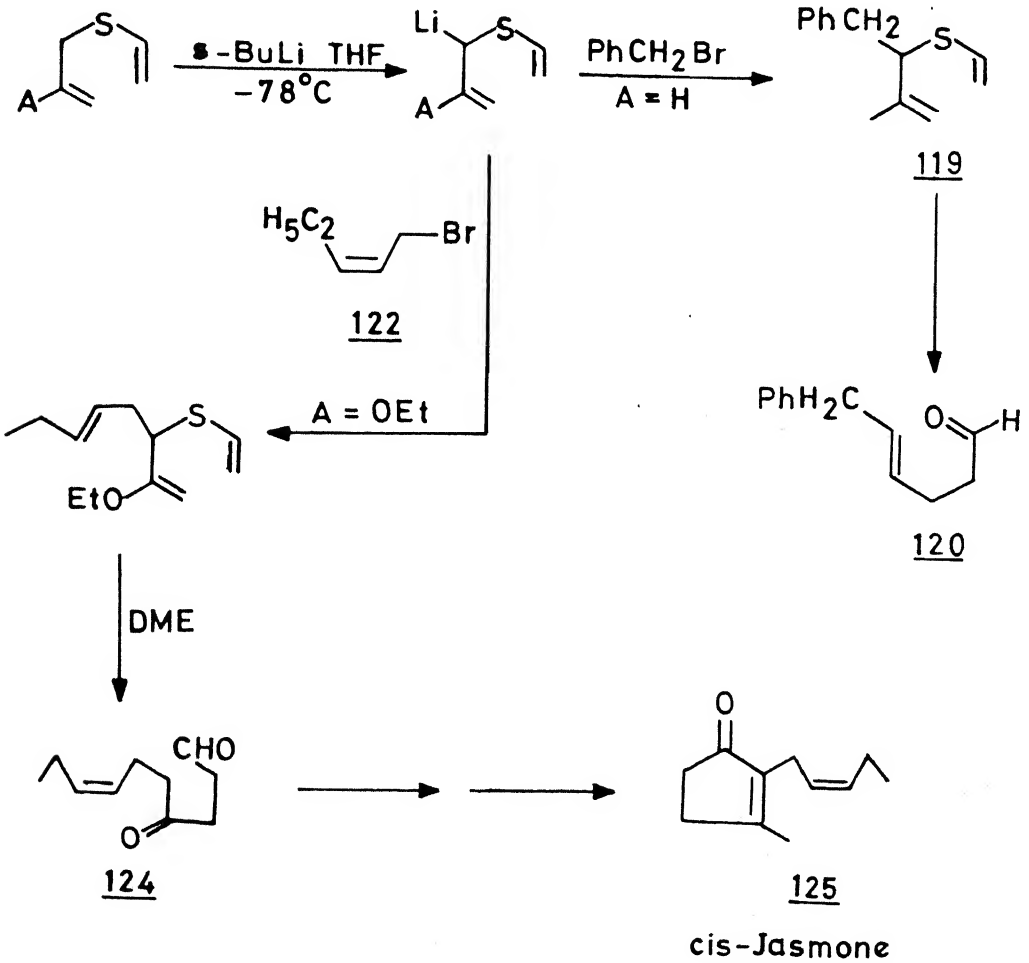


Figure 20

II.2 Results and Discussion

In the introduction part of this chapter importance of vinyl and allyl sulfides has been discussed by taking examples from the literature. Reductive and hydrolytic removal of sulfur as well as deprotonation of the allylic position, if available, of vinyl sulfides increases the importance of these compounds. Regioselective introduction of vinyl sulfide group eventually becomes important. Likewise allylic sulfides are also important intermediates where functional groups α or γ to the sulfur could be introduced. Therefore, synthesis of vinyl and allyl sulfides with different functional groups could be important and if these compounds are obtained in optically pure form their usefulness would be further increased. With this view in mind we have chosen to explore the potential of two sets of sulfur containing synthons viz. **126** ---> **129** (Fig. 21 and 22). These were so chosen so that they could be elaborated into useful intermediates. For converting these compounds into optically pure ones use of PLAP hydrolysis was explored. Synthesis of **126** and **127** were carried out according to literature procedure[30]. Thus, treatment of cyclopentanone with benzenesulphenyl chloride gave **126** in 60% yield. Likewise 2-phenylthio-2-cyclohexenone **127** was also prepared in 62% yield. Structures of these compounds were confirmed on the basis of their spectral data (cf. sec II.4). Reduction of **126** with $NaBH_4/CeCl_3.7H_2O$[31] in methanol gave the corresponding allyl alcohol which was acetylated using acetic anhydride-pyridine to obtain **130** in 92% yield. Its IR spectrum

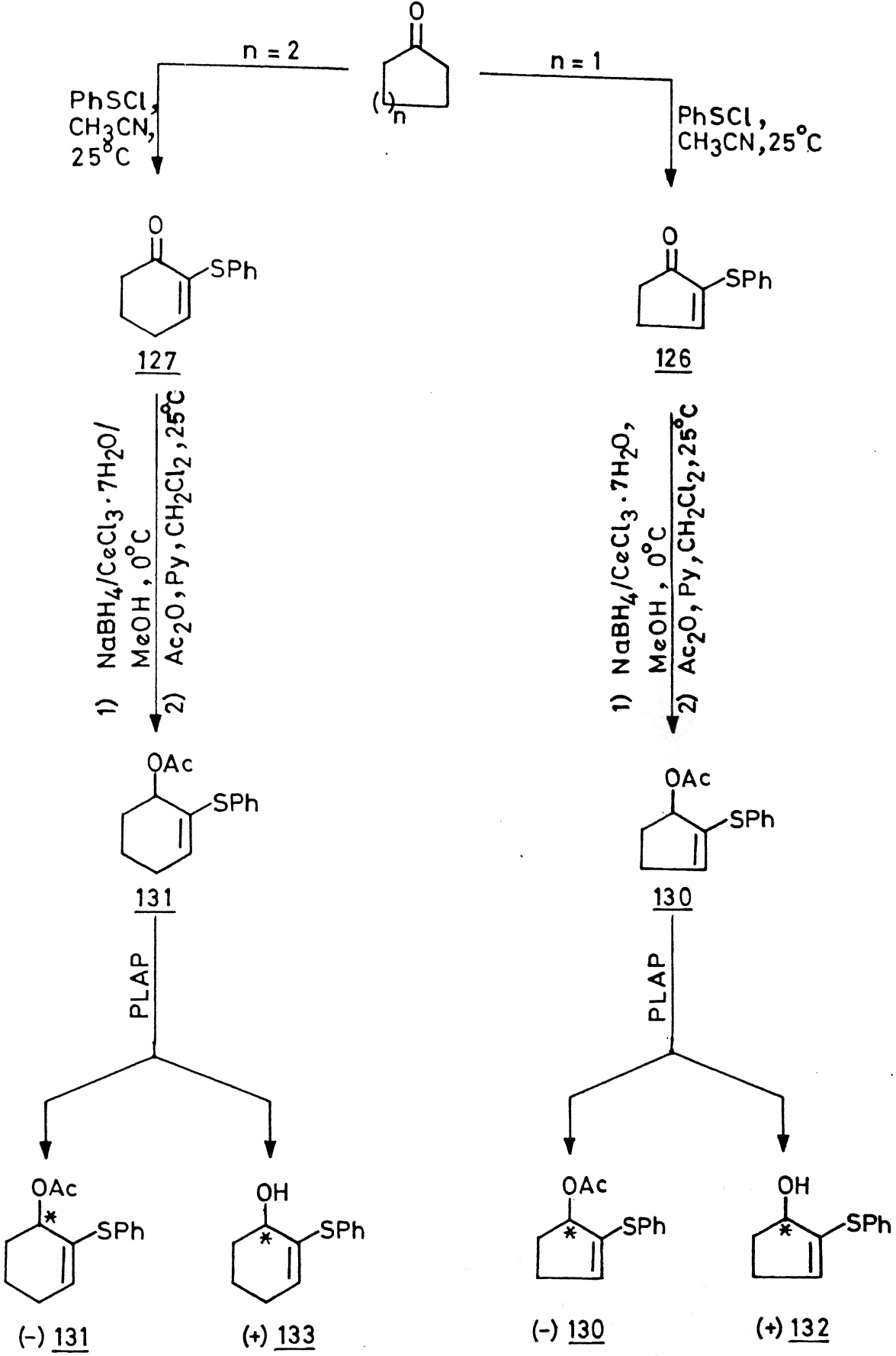

n = 2
n = 1
PhSCl, CH3CN, 25°C
PhSCl, CH3CN, 25°C
SPh
127
126
1) NaBH4/CeCl3·7H2O/ MeOH, 0°C
2) Ac2O, Py, CH2Cl2, 25°C
1) NaBH4/CeCl3·7H2O, MeOH, 0°C
2) Ac2O, Py, CH2Cl2, 25°C
OAc
SPh
131
130
PLAP
PLAP
OAc
OH
SPh
(-) 131
(+) 133
(-) 130
(+) 132

Figure 21

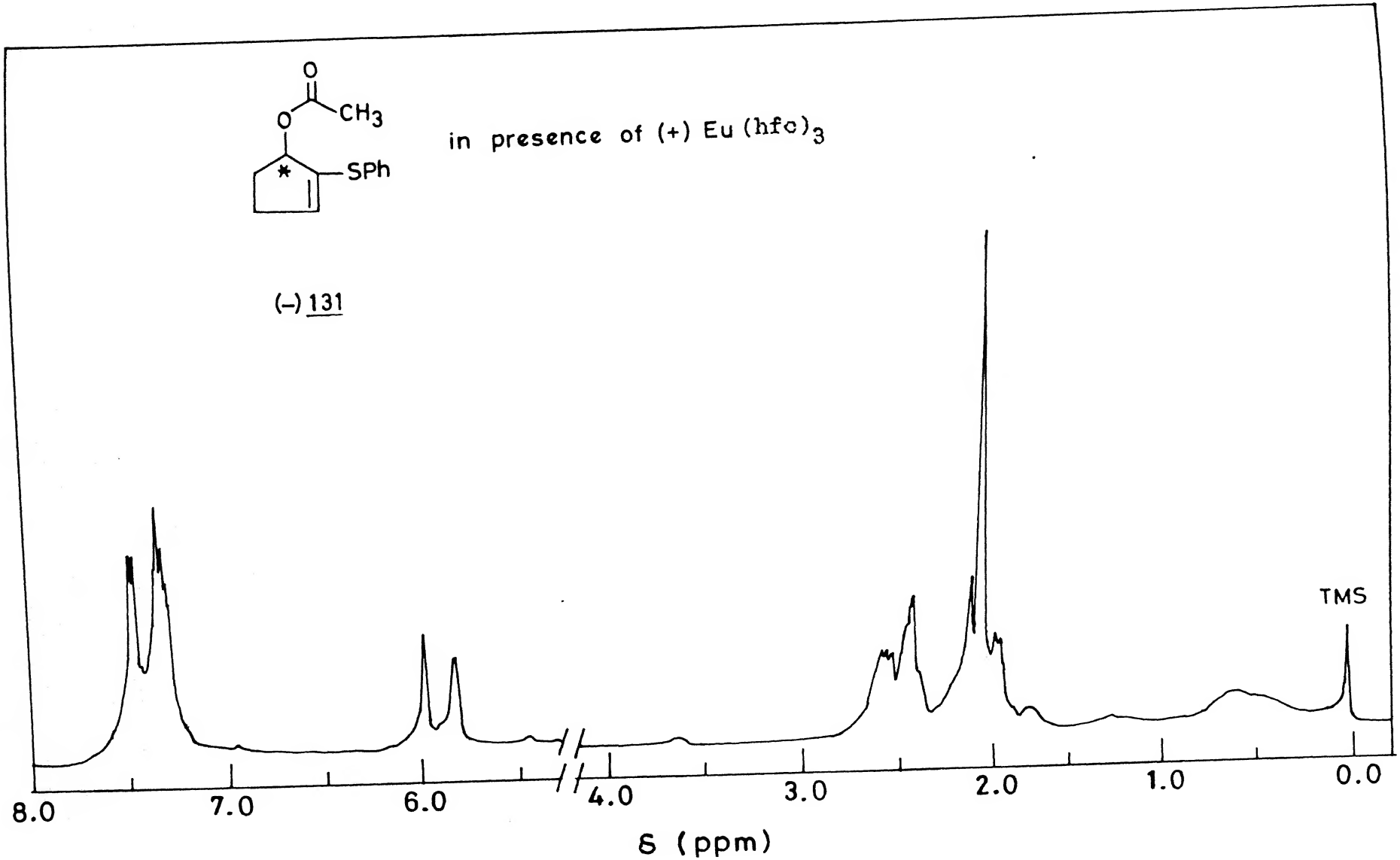


Figure II.1: ^{1}H NMR spectrum (400 MHz) of (-) **131**

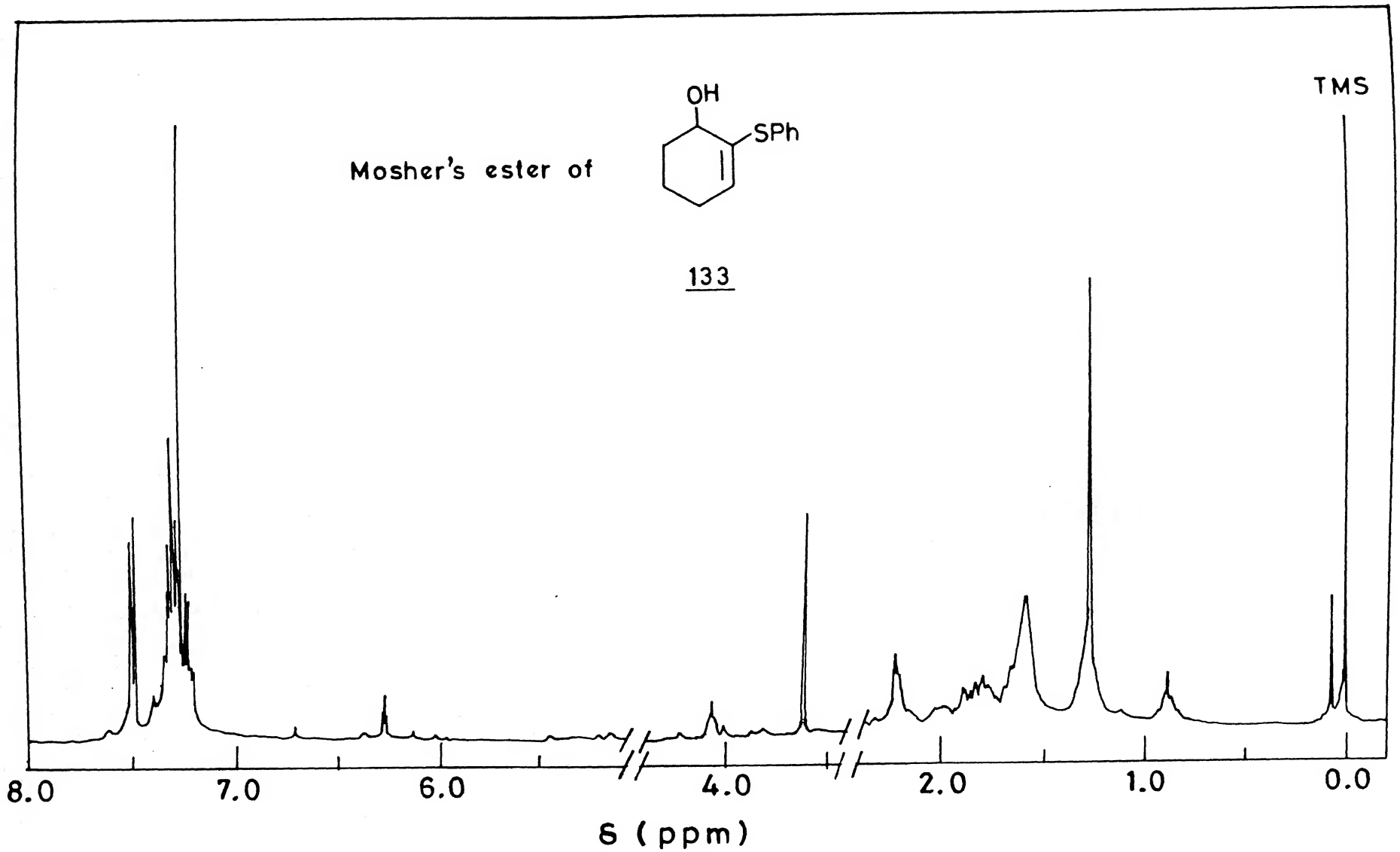


Figure II.2: ^{1}H NMR spectrum (400 MHz) of (+) **133**

showed a strong peak at 1725 ($\nu_{C=O}$) cm^{-1} and the ^1H NMR gave signals at δ 1.87 (3H, s, -O-$COCH_3$), 1.7-2.7 (4H, m, allylic and other methylenes), 5.33-5.73 (1H, m, -CHOAc), 5.73-5.9 (1H, d, = CH, J = 3 Hz), 7.0-7.77 (5H, m, aromatic protons). In order to make further use of this compound we considered the possibility of enzymatic resolution of this racemic vinyl sulfide. The crude pig liver acetone powder (PLAP) based resolution as described in section I.20, were attempted. The resolved alcohol **132** was obtained in 54% yield. The 400 MHz ^1H NMR spectrum of its Mosher's ester showed it to be 96% enantiomerically pure. Its rotation value was found to be $[\alpha]^{25}_D$ = (+) 46.27 (C1, $CHCl_3$). On the other hand the recovered acetate showed $[\alpha]^{25}_D$ = (-) 17.475 (C1, $CHCl_3$), which was found to have 53% enantiomeric excess. This was confirmed on the basis of its ^1H NMR spectral analysis in the presence of (+) Eu(hfc)$_3$.

Likewise compound **127** was also reduced by $NaBH_4$/ $CeCl_3.7H_2O$ and acetylated to obtain **131** in 95% yield. The spectroscopic data of **131** was consistent with its structure (cf. sec II.5). Its enzymatic resolution with PLAP gave 77% of the resolved alcohol whose rotation value was found to be $[\alpha]^{25}_D$ = (+) 93.75 (C1, $CHCl_3$). ^1H NMR spectral analysis of its Mosher's ester revealed e.e of it to be 81%. The corresponding acetate was on the other hand only 34% enantiomerically pure, with rotation value $[\alpha]^{25}_D$ = (-) 58.733 (C1, $CHCl_3$).

Since the optical purity of the resolved alcohols **132** and **133** were appreciably high we turned our attention to find out how the allyl acetates with an allylic sulfide group behave

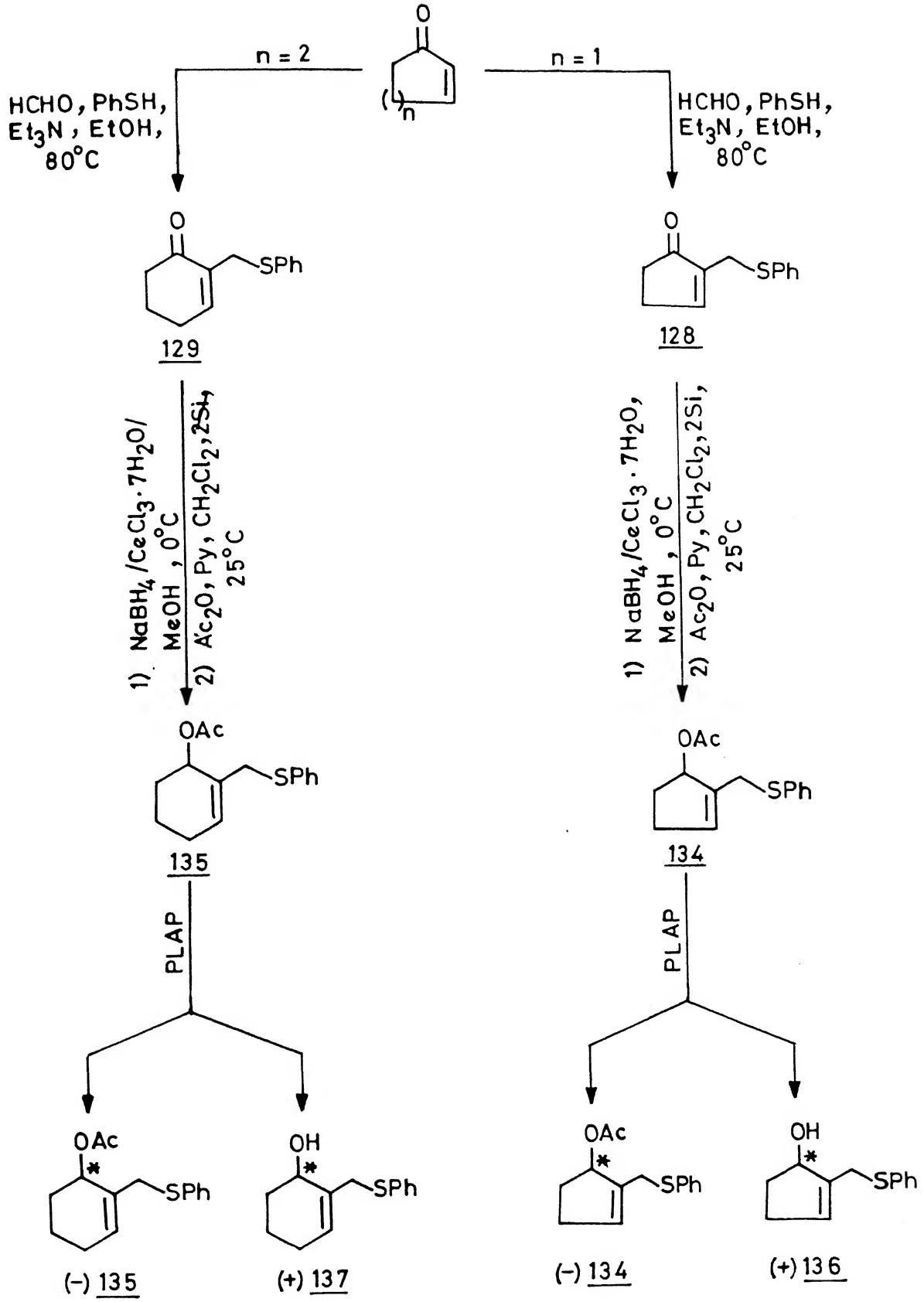

n = 2
n = 1
HCHO, PhSH, Et3N, EtOH, 80°C
HCHO, PhSH, Et3N, EtOH, 80°C
SPh
129
128
1) NaBH4/CeCl3·7H2O/ MeOH, 0°C
2) Ac2O, Py, CH2Cl2, 25°C
OAc
135
134
PLAP
OH
(-) 135
(+) 137
(-) 134
(+) 136

Figure 22

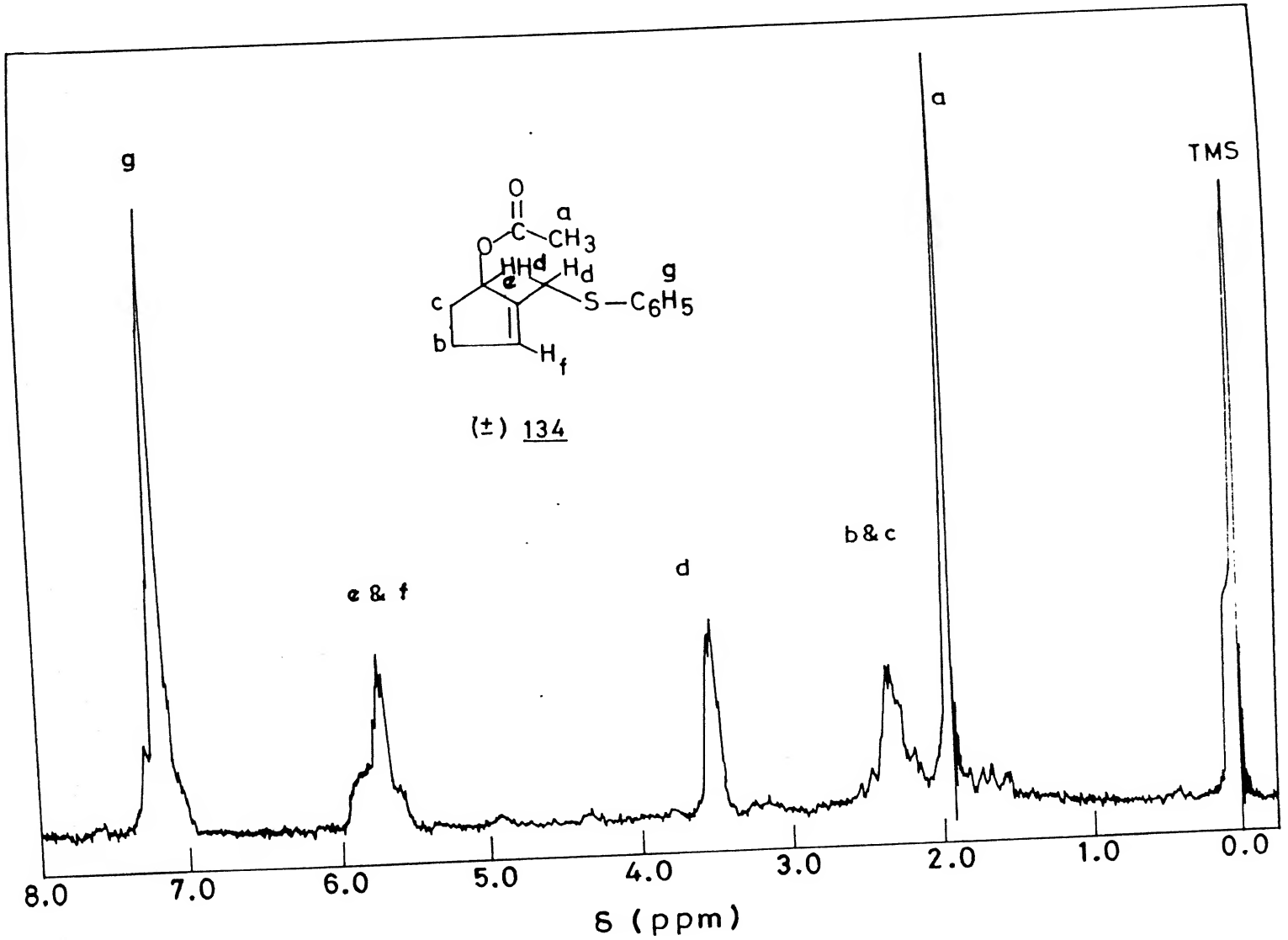


Figure II.3: ^{1}H NMR spectrum (60 MHz) of (±) **134**

towards enzymatic resolution. For this purpose substrates **128** and **129** were prepared following a literature procedure[32]. Thus, treatment of cyclopentenone with thiophenol, formaldehyde and triethylamine gave 2-[phenylthio(methyl)]-2-cyclopentenone **128**. Its ^{1}H NMR spectrum showed δ 2.13-2.73 (4H, m, methylenes), 3.4-3.73 (2H, d, $-CH_2SPh$, J = 2 Hz), 7-7.5 (6H, m, aromatic and vinylic protons). The IR spectrum showed a strong peak at 1690 ($\nu_{C=O}$), 1620 ($\nu_{C=C}$) and 1570 ($\nu_{aromatic}$) cm^{-1}. Its mass spectrum gave (M^+) and $(M + 1)^+$ peaks at m/z 204 and 205 respectively. Reduction of **128** with $NaBH_4/CeCl_3.7H_2O$, as described above[31] for compounds **126** and **127**, gave the corresponding alcohol whose acetylation (cf. sec II.7) gave the required acetate **134** in 78% yield. Its structure was confirmed from its spectroscopic and analytical data. Thus, its ^{1}H NMR spectrum showed peaks at 1.3-2.5 (4H, m, methylenes), 1.93 (3H, s, $-O-CO-CH_3$), 3.5 (2H, d, $-CH_2SPh$, J = 3 Hz), 5.5-5.87 (2H, m, $-CHOAc$ and $=CH-$), 6.93-7.3 (5H, m, aromatic protons). Its IR showed a strong peak at 1720 ($\nu_{-O-CO-CH_3}$) cm^{-1} and its Mass spectrum showed peak at m/z 248 (M^+). The enzymatic hydrolysis using PLAP gave the corresponding resolved alcohol only in 34% yield with $[\alpha]^{25}_D$ = (+) 18.226 (C1, $CHCl_3$). It was found to be 74% enantiomerically pure on the basis of ^{1}H NMR spectral analysis of its Mosher's ester. The unhydrolysed acetate was analysed on the basis of its ^{1}H NMR (400 MHz) spectral analysis using shift reagent (+) $Eu(hfc)_3$ and found to have 30% e.e.

Likewise 2-[phenylthio(methyl)]-2-cyclohexenone **129** was prepared from cyclohexenone, thiophenol, formaldehyde and triethylamine in 63% yield. The spectral and analytical data

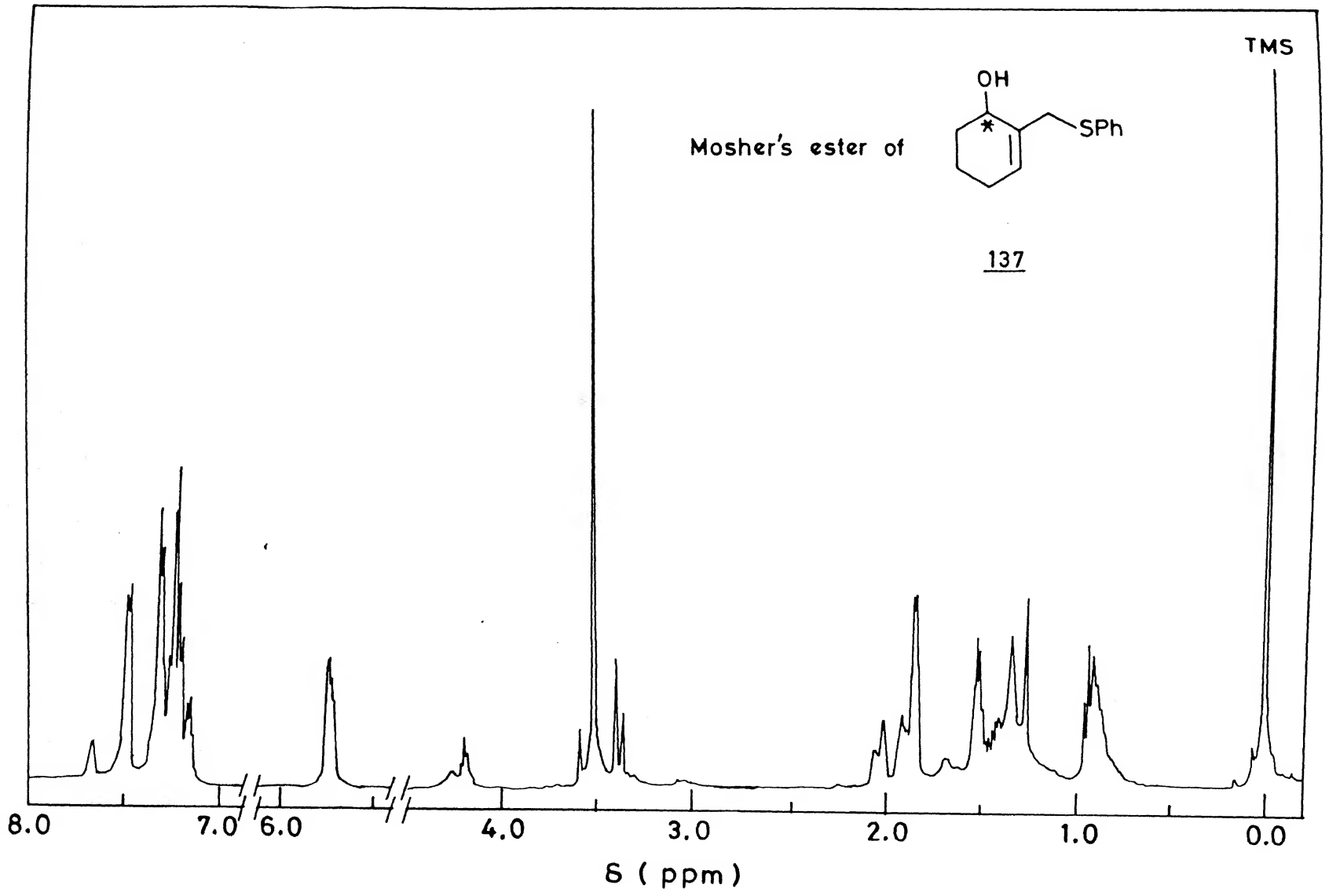
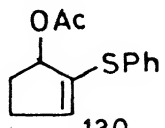
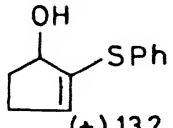
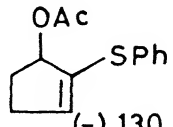
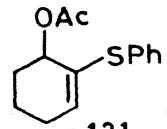
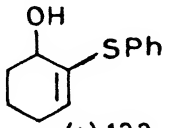
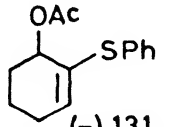
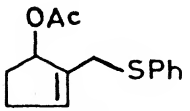
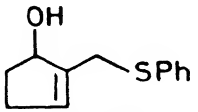
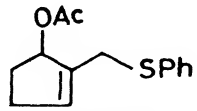
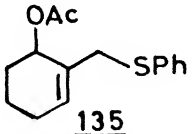
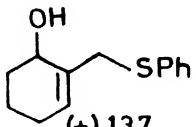
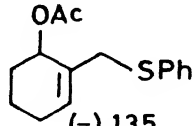


Figure II.4: ^{1}H NMR spectrum (400 MHz) of (+) **137**

Table-I

PLAP Catalysed Hydrolysis

Entry	(±) Acetoxy Ester	Chiral Hydroxy Ester			Chiral Acetoxy Ester		
		Compound	$[\alpha]_D^{25}$	e.e.	Compound	$[\alpha]_D^{25}$	e.e.
1	 130	 (+) 132	(+) 46.279 ($C1, CHCl_3$)	96 %	 (-) 130	(-) 17.475 ($C1, CHCl_3$)	53 %
2	 131	 (+) 133	(+) 93.750 ($C1, CHCl_3$)	81 %	 (-) 131	(-) 58.733 ($C1, CHCl_3$)	34 %
3	 134	 (+) 136	(+) 18.226 ($C1, CHCl_3$)	74 %	 (-) 134	(-) 8.428 ($C1, CHCl_3$)	30 %
4	 135	 (+) 137	(+) 26.017 ($C1, CHCl_3$)	75 %	 (-) 135	(-) 15.091 ($C1, CHCl_3$)	40 %

(cf. sec II.6) for this compound were in agreement with the structure assigned to it. Reduction of this compound with $NaBH_4/CeCl_3.7H_2O$ gave the corresponding alcohol which was connected into its acetate **135** using standard acetylation condition (cf: sec. II.7). Its ^1H NMR spectrum showed peaks at δ1.47-2.1 (6H, m, methylenes) 1.92 (3H, s, -O-CO-CH_3), 3.37(2H, s, -CH_2-SPh), 5.17-5.47 (1H, m, -CHOAc), 5.53-5.77 (1H, br. t, =CH-), 6.97-7.33 (5H, br. s, aromatic protons). The enzymatic resolution of **135** with PLAP was performed for 72 hrs to obtain the resolved alcohol in 79% yield with rotation value as $[\alpha]^{25}_D$ = (+) 26.017 (C1, $CHCl_3$). Its enantiomeric purity was found to be 75% from the ^1H NMR spectral analysis of its Mosher's ester. The unhydrolysed acetate was found to possess 40% enantiomeric purity and its rotation value was found to be $[\alpha]^{25}_D$= (-) 15.091 (C1, $CHCl_3$).

The above study clearly indicates that the substrates chosen viz **130, 131, 134, 135** for the enzymatic hydrolysis are capable of undergoing resolution. When sulfur is closer to the asymmetric centre the resolution appears to be better. The absolute configuration of these optically active alcohols however need to be determined. Attempts to desulfurise these alcohols as well as the acetates were not successful.

Synthesis of compound **129** required, according to the literature procedure[32], addition of extra amount of formaldehyde after 24 hrs and the refluxing continued till cyclohexenone is consumed. Interestingly a very polar compound was found to form at the end of the reaction. When a large excess of formaldehyde was added this polar compound kept on increasing and the

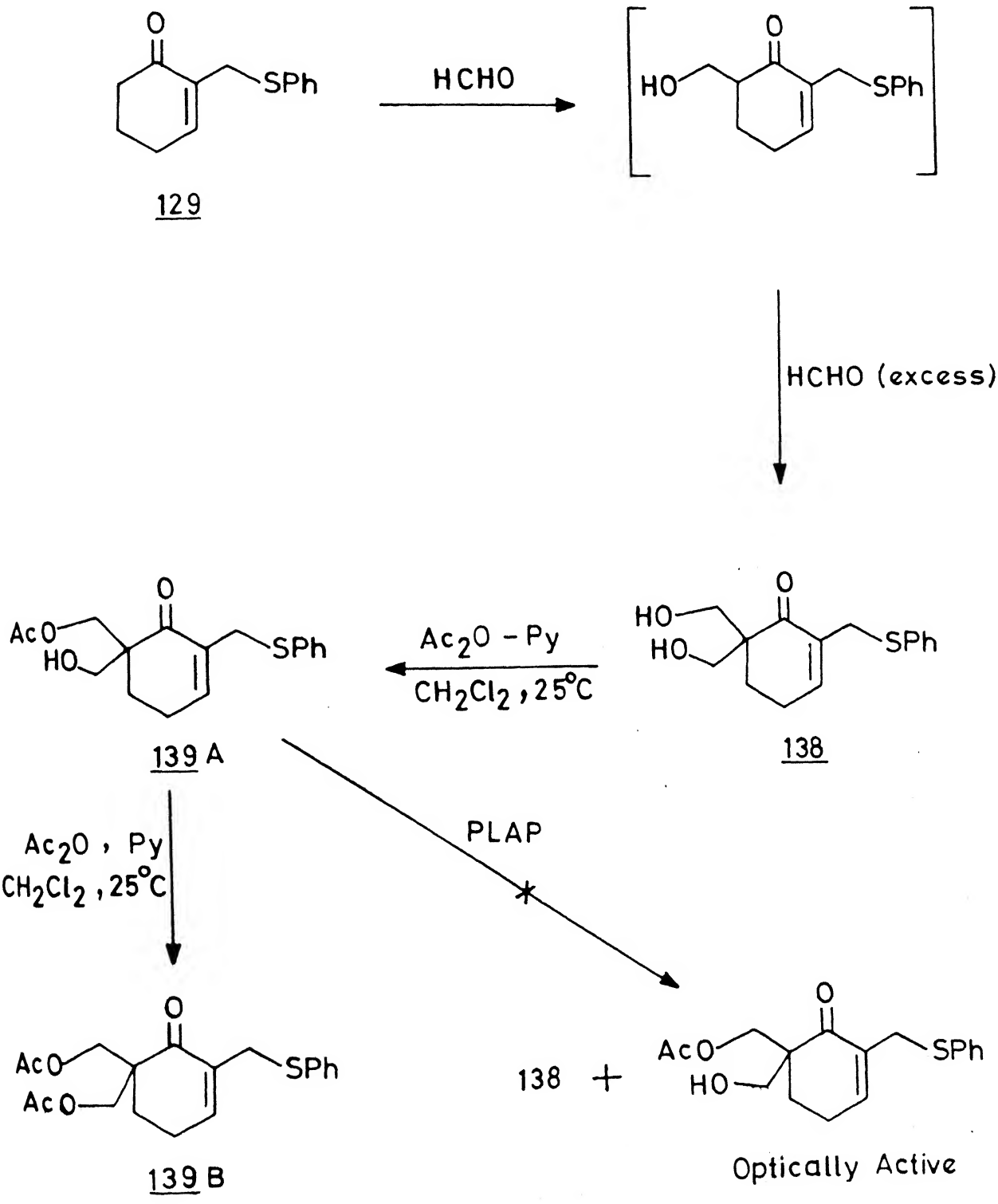

O
SPh
HCHO
HO
129
HCHO (excess)
AcO
Ac2O - Py
CH2Cl2, 25°C
139 A
138
Ac2O, Py
CH2Cl2, 25°C
PLAP
139 B
138 +
Optically Active

Figure 23

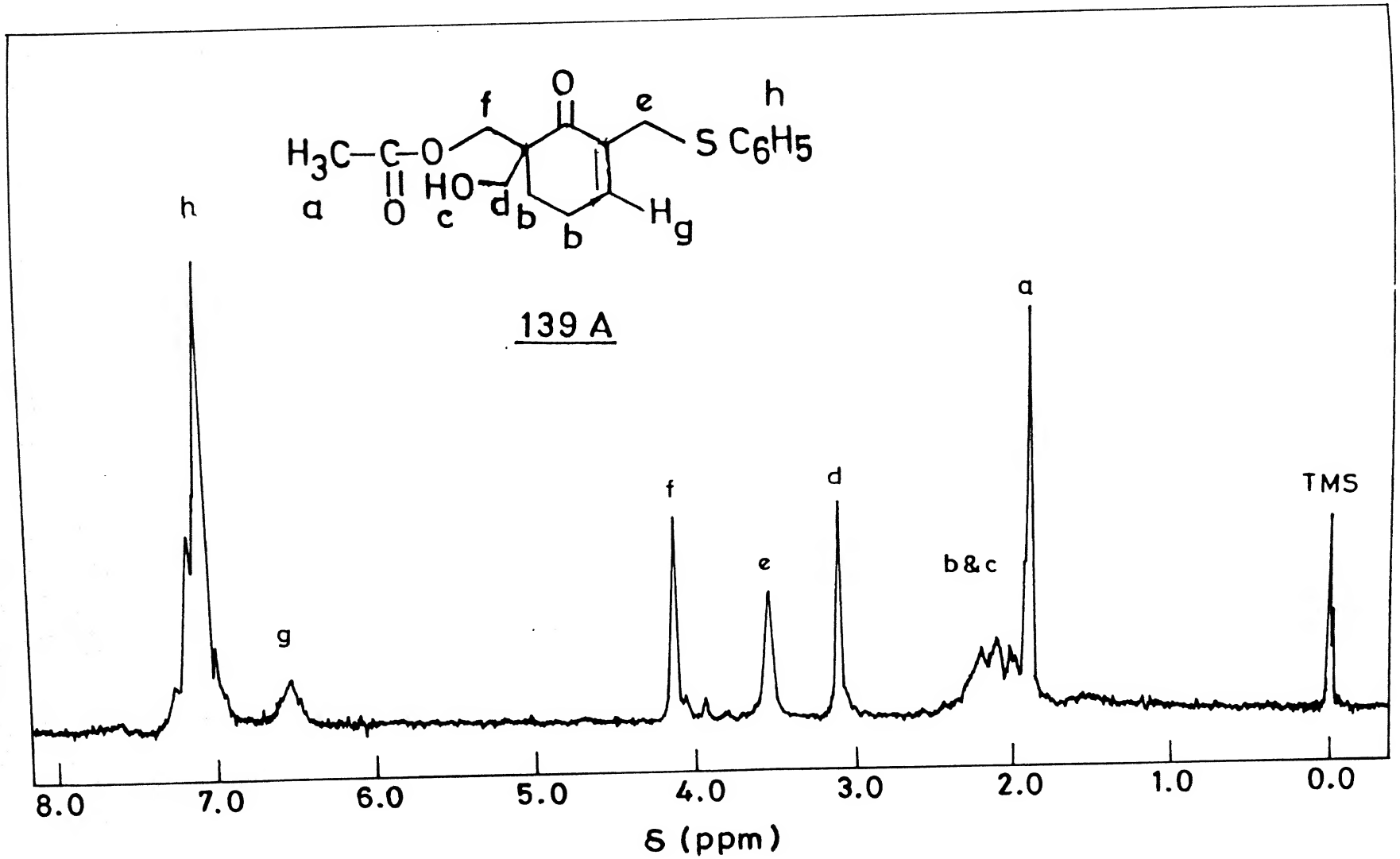


Figure II.5: ^{1}H NMR spectrum (60 MHz) of **139A**

2-[phenylthio(methyl)]-2-cyclohexenone kept on decreasing as was noticed by thin layer chromatographic analysis of the reaction mixture. The polar nature of this product suggested it to be an alcohol and so the crude product was acetylated. The spectral analysis of this acetylated product indicated that it has structure **139A** (Fig. 23). Evidently compound **129** has undergone hydroxymethylation twice on the adjacent methylene carbon to yield the diol **138**. The IR spectrum of **139A** showed two characteristic peaks 1720 ($\nu_{C=O}$), 1570 ($\nu_{C=C}$) cm^{-1}. The ^1H NMR spectrum showed signals at δ 1.83-2.5 (4H, m, methylenes), 1.93 (3H, s, $-OCOCH_3$), 3.13 (2H, s, $-CH_2OH$), 3.6 (2H, br.s, $-CH_2-SPh$), 4.17 (2H, s, $-CH_2OAc$), 6.6 (1H, br. t, $>C = CH$), 6.83-7.4 (5H, m, aromatic). Its mass spectrum showed M^+ peak at (m/z) 320 (M^+) and 302 ($M^+ - H_2O$). This is an interesting compound as it represents a class of compounds possessing a quaternary centre. Surprisingly, however, further acetylation of **139A** was extremely sluggish. Ideally **139B** is a good compound for PLAP hydrolysis to obtain **139A** in optically pure form. But since **139B** was not easily obtained the PLAP hydrolysis could not be performed on this substrate. In order to find out the behaviour of such compounds towards PLAP hydrolysis compound **139A** itself was subjected to PLAP hydrolysis. However, no clean hydrolysis was found to occur and a number of compounds seemed to form during this reaction.

To make further uses of compound **126** a few more experiments were carried out to synthesise some interesting synthons. Since allylic oxidation to obtain oxygenated compound is well known in the literature[33], we considered the possibility of obtaining **141**

(Fig. 24). For this purpose compound **126** was treated with NBS in the presence of catalytic amount of AIBN. This resulted in formation of the bromoenone **140** (Fig. 24) which was immediately reacted with silver acetate in acetic acid to obtain **141** in 59% yield. In its IR spectrum strong peaks at 1720 ($\nu_{C=O}$), 1740 (ν_{O-COCH}) cm^{-1} were observed. In its ^1H NMR spectrum peaks at δ: 1.93 (3H, s, -O-COCH_3), 2.26 (1H, d.d, -C(H_c)(H_b)-CH_d(OAc), J = 16 Hz, J = 3 Hz), 2.9 (1H, d. d, - C(H_c)(H_b) - CH_d (OAc), J = 16 Hz, 9 Hz), 5.5 (1H, m, -CH_dOAc), 6.27 (1H, d, = CH_b- , J = 3 Hz), 7.32 (5H, m, aromatic) were observed. Mass spectrum showed M^+ at m/z 248.

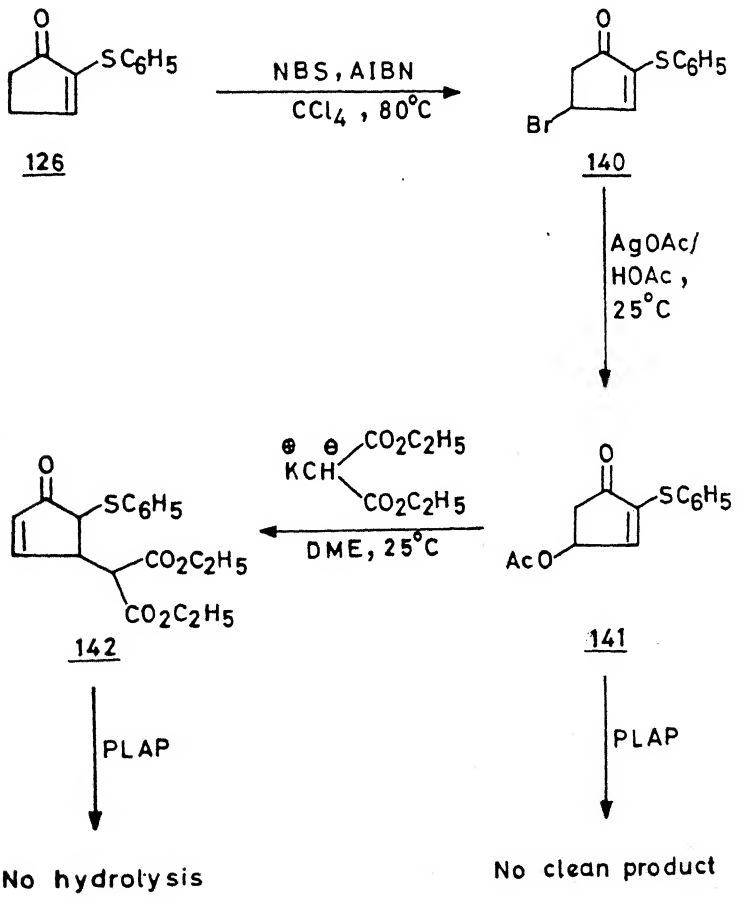


Figure 24

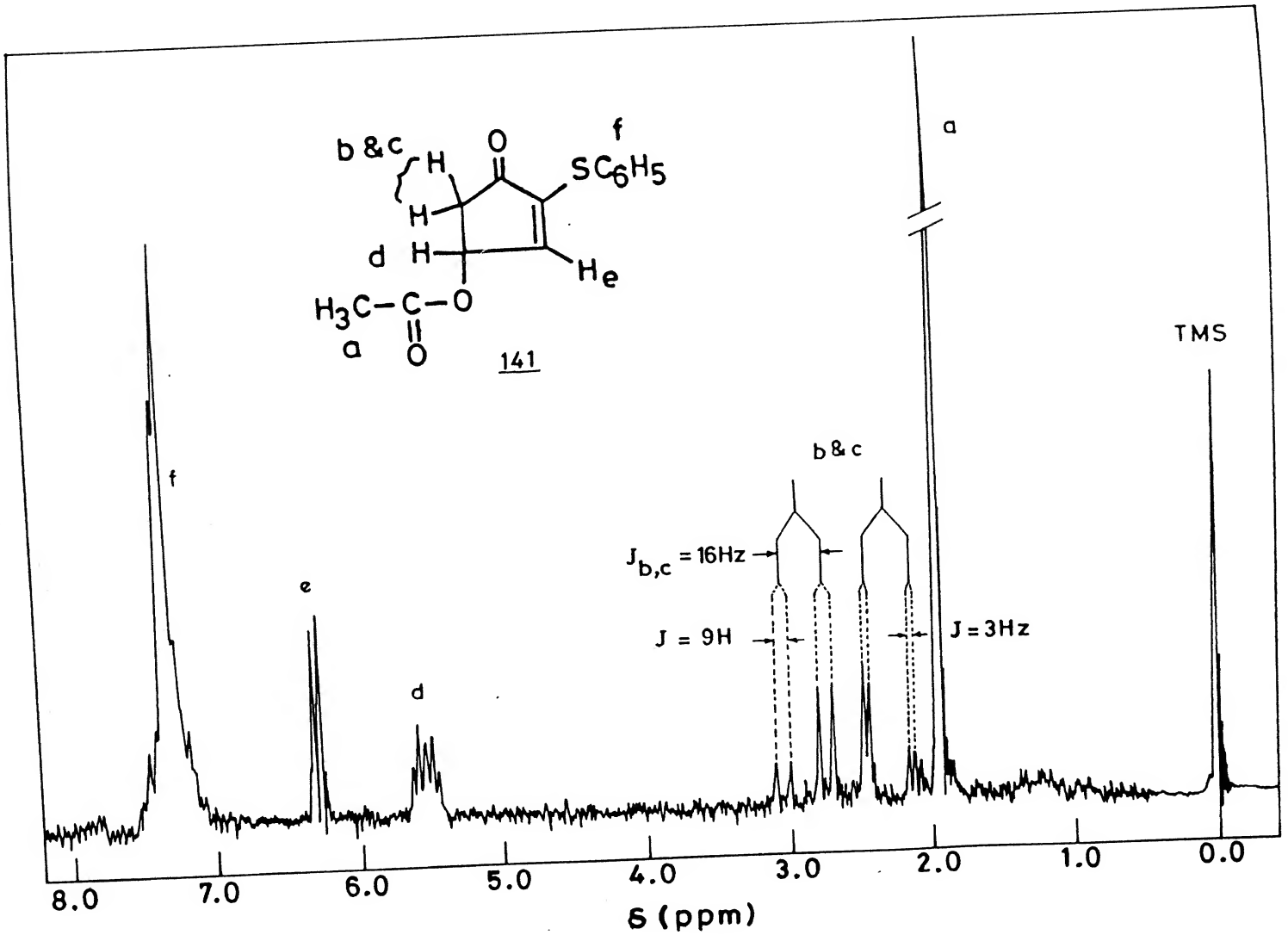


Figure II.6: ^{1}H NMR spectrum (60 MHz) of **141**

Having obtained compound **141**, PLAP based resolution was attempted to obtain the corresponding hydroxy compound in optically pure form. However, this compound was sluggish towards hydrolysis and whatever small amount of the products appeared to form was a complex mixture of several compounds. It is probable that the sensitive enone system perhaps was responsible for the failure of the hydrolysis. In order to further explore the potential of **141** its reactions with a variety of nucleophiles were attempted. Initial attempts to react **141** with morpholine and benzyl alcohol under basic condition gave a complex mixture of products. On the other hand, reactions with a softer anion viz diethylmalonate anion was found to be cleaner. It gave a product **142** whose spectral analysis indicated it to have a structure **142** (Fig. 24). The IR spectrum of this compound showed a broad strong peak at 1730 ($\nu_{C=O}$) and its ^1H NMR spectrum showed signals at 1.23 (6H, 2t, -O-CH_2CH_3, J = 7Hz), 3.13-3.6 (3H, m, methines), 4.13 (4H, 2q, -O-CH_2CH_3, J = 7 Hz), 6.07 (1H, d. d, CH=CH-CO-, J = 2Hz, 6 Hz), 6.6-7.67 (6H, m, aromatic protons and -COCH=CH-). Mass spectrum showed M^+ peak at (m/z) 348. Formation of the product could be explained via Michael addition of the diethylmalonate anion followed by elimination of the acetate ion as shown in (Fig. 25). This has a literature precedence[34] of similar compounds but without thiophenyl moiety. Compounds of this type **142** have strong structural resemblance with prostaglandins[35] **143, 144, 145** (Fig. 26) and therefore if they are obtained in optically pure form it would be very useful. To this effect PLAP hydrolysis of this diester **142** was attempted. But once again this compound was

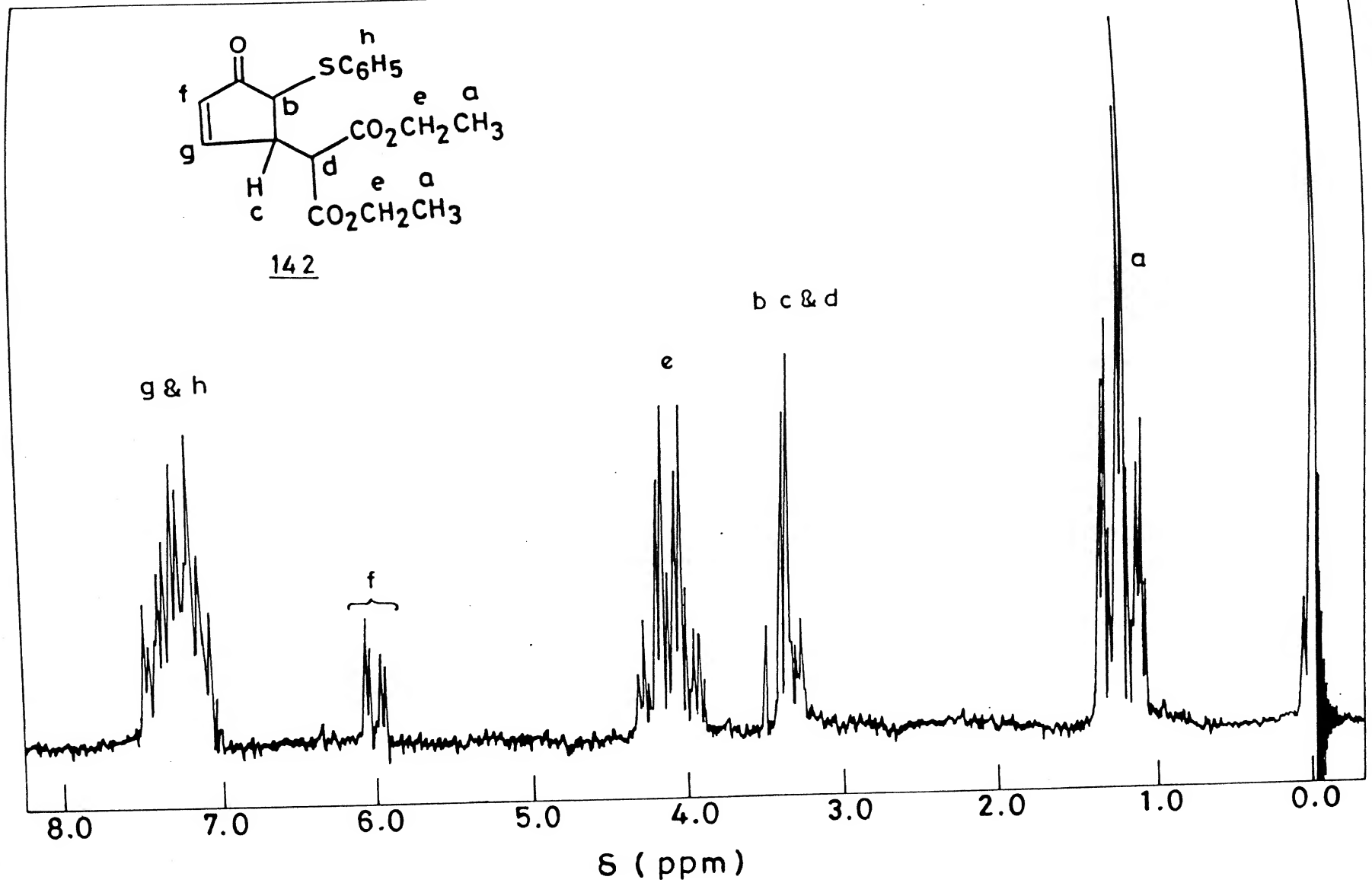


Figure II.7: ^{1}H NMR spectrum (60 MHz) of **142**

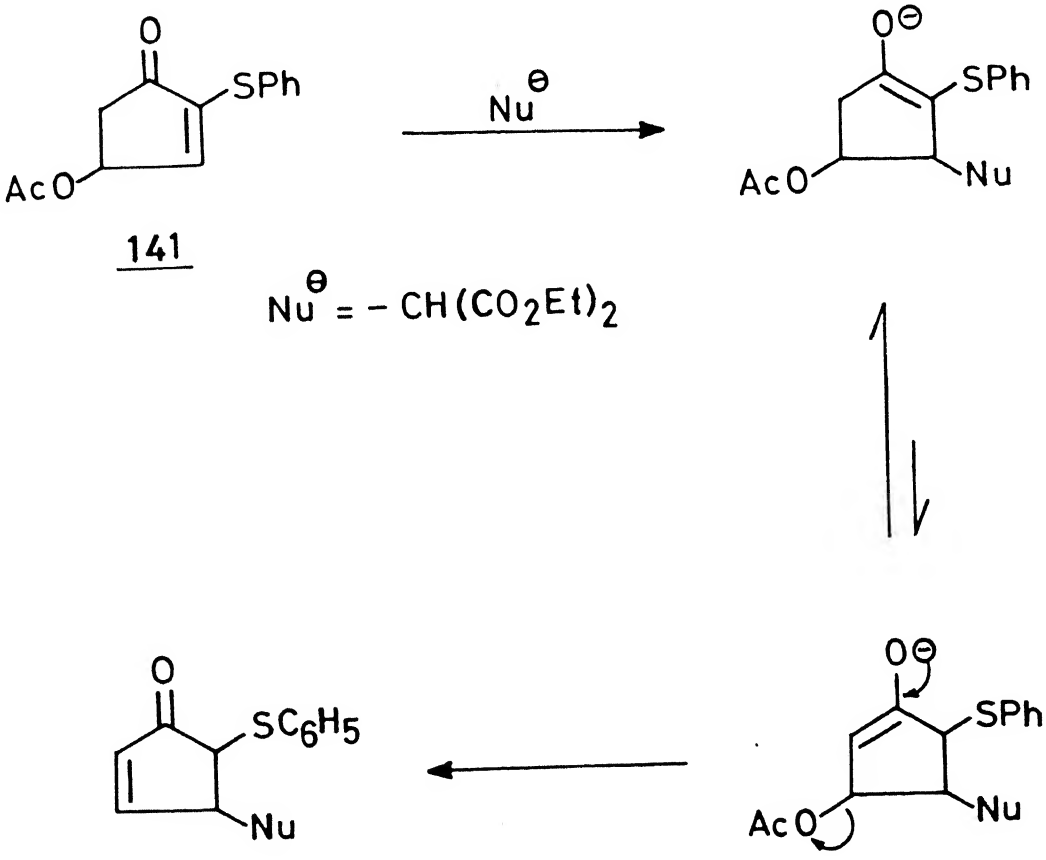
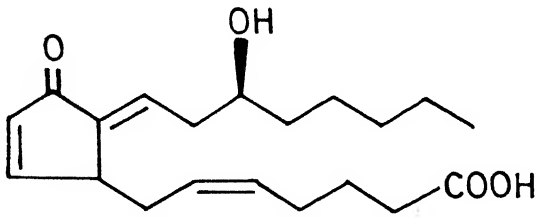
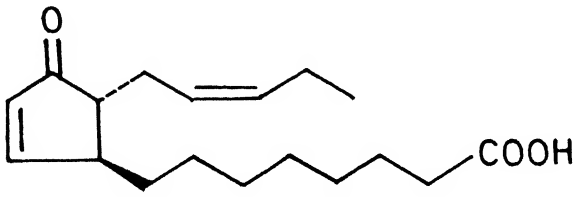

O
SPh
AcO
Nu⊖
O⊖
SPh
AcO
Nu
141
Nu⊖ = – CH(CO2Et)2
O⊖
SPh
AcO
Nu
O
SC6H5
Nu
142

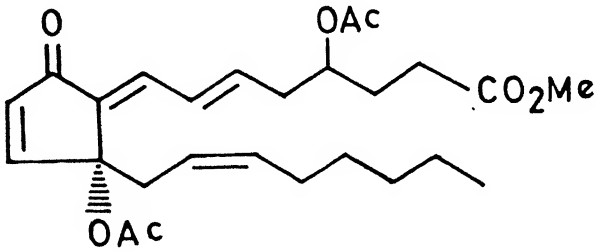
Figure 25



143



144



145

Figure 26

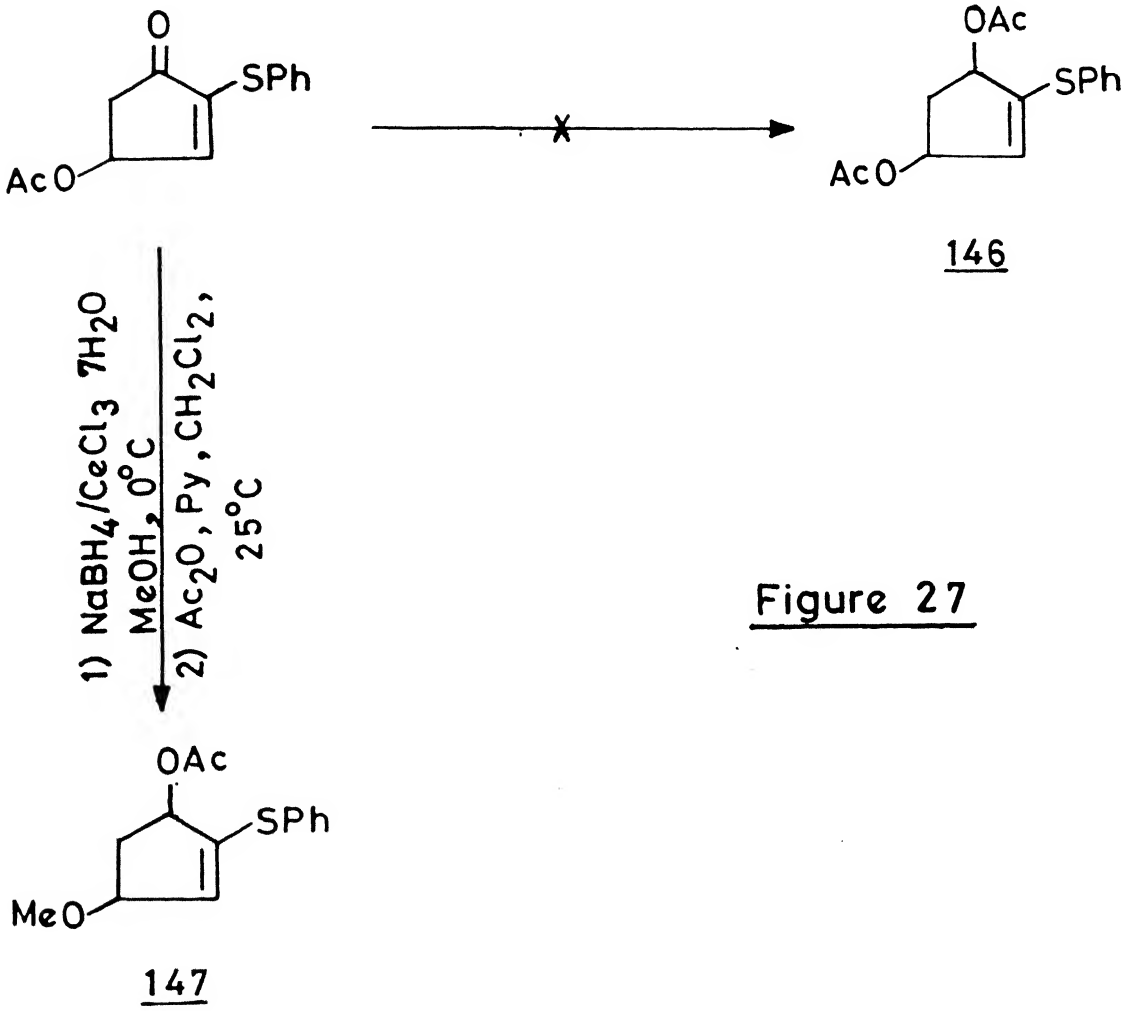

O
SPh
AcO
X
OAc
SPh
AcO
146
1) NaBH4/CeCl3 7H2O
MeOH, 0°C
2) Ac2O, Py, CH2Cl2,
25°C
OAc
SPh
MeO
147

Figure 27

found to be inert towards PLAP hydrolysis. This again proves that presence of an enone moiety somehow interferes in the reaction, and prevents the hydrolysis. To further modify the structural aspects of this enone **141** it was reduced with $NaBH_4/CeCl_3.7H_2O$ in methanol so that upon acetylation one could obtain the diacetate **146** (Fig. 27) for further PLAP based hydrolytic studies. However, the product obtained in 30% yield from the reduction followed by acetylation was not the expected diacetate **146** but instead it had the structure **147** (Fig. 27). The ^1H NMR spectrum clearly supported the structural assignment. Thus it showed signals at δ 1.75-3.0 [5H, m, methylenes and a

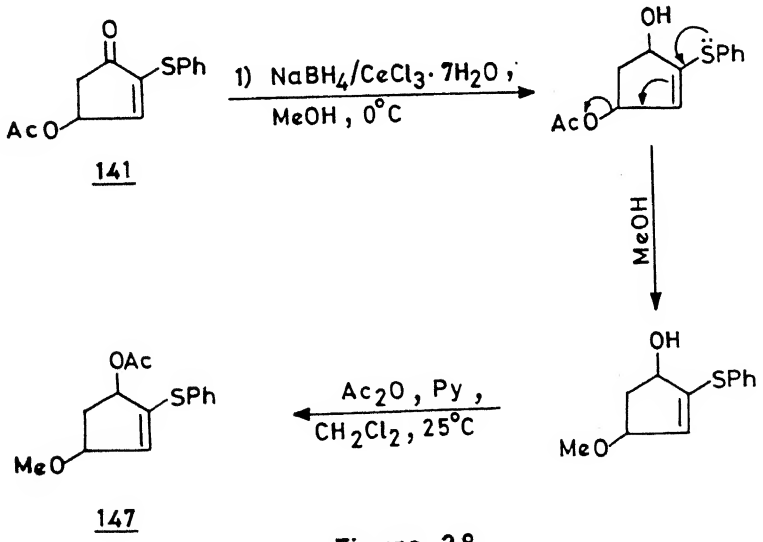


Figure 28

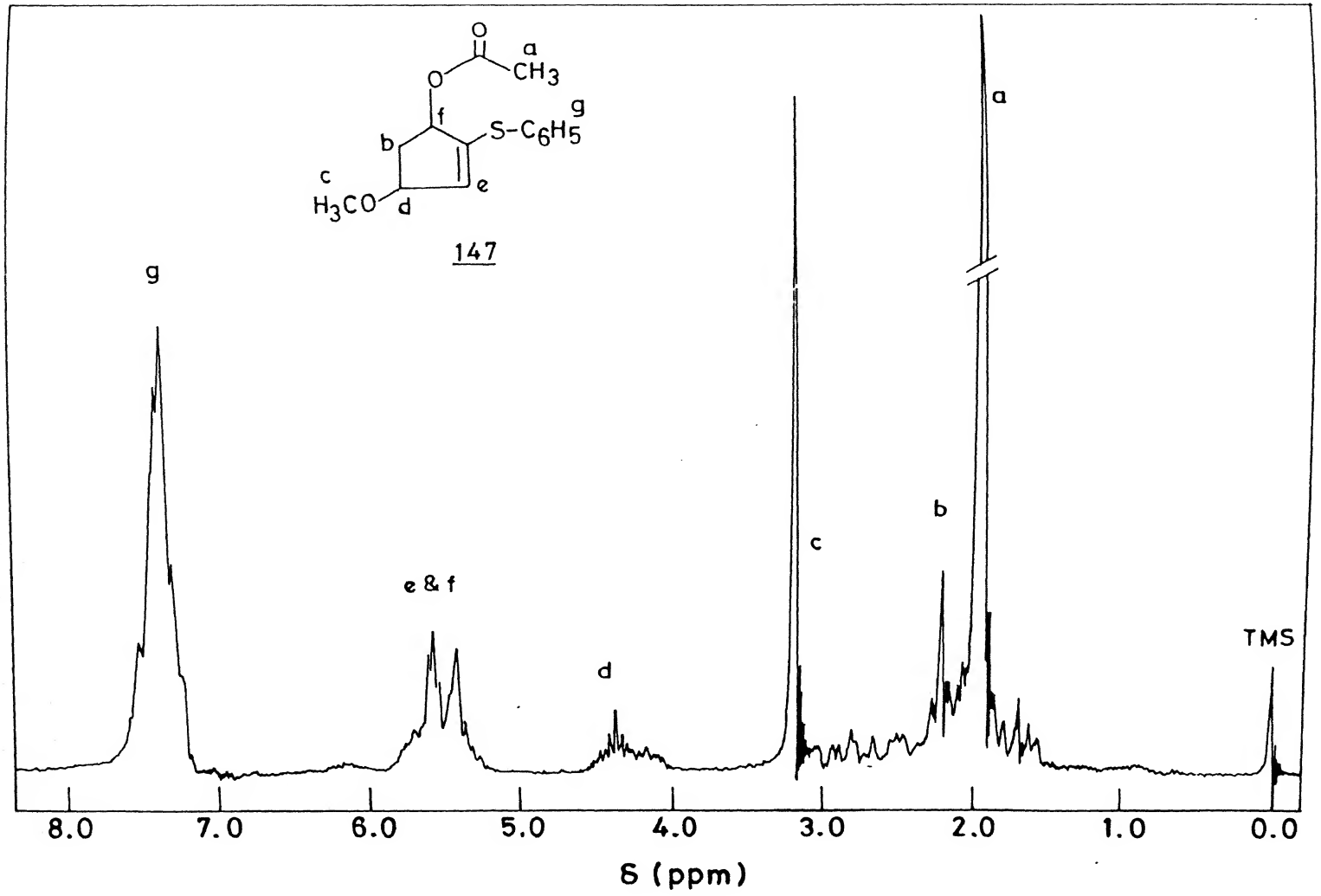


Figure II.8: ^{1}H NMR spectruum (60 MHz) of **147**

peak at δ 1.93 (3H, s, -O-$COCH_3$)], 3.13 (3H, s, -OMe), 3.93-4.47 (1H, m, -CHOMe), 5.1-5.73 (2H, m, -CHOAc, =CH), 6.93-7.5 (5H, m, aromatic protons). In its IR spectrum strong peak at 1720 ($\nu_{C=O}$) was observed. Furthermore since the product **147** was obtained in less yield further studies were not carried out. Reduction of **141** was also attempted in nonhydroxylated solvent such as THF and dioxane, however, the reactions were not found to be clean. Formation of **147** could be explained as shown in the Fig. 28. PLAP hydrolytic study on this compound was, therefore, not conducted.

The above studies have led to the synthesis of some very useful sulfur containing chiral and achiral synthons for organic synthesis. Experimentations to improve the yields in some cases and PLAP hydrolytic studies under modified conditions and the use of other enzymes are needed to be explored.

II.3 Experimental Procedure

The details of the instruments used are the same as described in section I.4. CH_3CN was dried by using 4Å molecular sieves and CaH_2 and finally distilled over CaH_2. Dry CCl_4 was prepared by distilling it over P_2O_5. Acetic acid was freshly distilled before use. Dimethoxyethane (DME) was dried using solid NaOH beads and $LiAlH_4$. NBS (N-bromo succinimide) and AIBN (2,2'-azo-bis isobutyronitrile) were recrystallised from water and ethanolic water (85:15) respectively. Benzenesulfenyl chloride was prepared from diphenyl disulphide and sulfuryl chloride following the literature procedure[36]. Cyclopentenone and cyclohexenone were prepared according to the literature procedure[37].

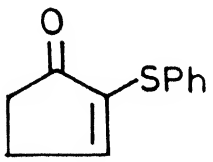
II.4 Preparation of 2-phenylthiocycloalk-2-enone

General procedure: Freshly distilled benzenesulfenyl chloride (15.8 g, 0.11 mol) was added dropwise to a solution of cycloalkanone (0.036 mol) in dry CH_3CN (60 ml) at 20°C during 1 hr. Then it was allowed to stir at room temperature for 4-5 hr. After cooling in an ice water bath, fine crystals of diphenyl disulphide appeared which were filtered off and washed with ice cold CH_3CN. The filtrate was evaporated under reduced pressure and boiled methanol (30 mL) was added to the residue and the

mixture reevaporated under vaccum. The whole process was repeated for a second time. Purification of the oily residue by column chromatography (petether: ethyl acetate = 97:3) gave 2-phenylthiocycloalk-2-enone.

The characteristics of 2-phenylthiocycloalk-2-enones are described below:

2-Phenylthiocyclopent-2-enone: (126)



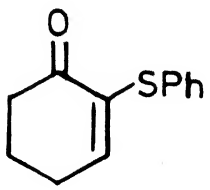
Light yellow coloured oil

Yield 60%

IR spectrum (neat) ν_{max} : 1700 (>C = O) cm^{-1}

^1H NMR spectrum (CCl_4): δ 7.5-7.2 (5H, m, aromatic protons), 6.9-6.75 (1H, t, = CH, J = 3 Hz), 2.7-2.32 (4H, m, allylic and other methylenes)

2-Phenylthiocyclohex-2-enone: (127)



Light yellow coloured oil

Yield 62%

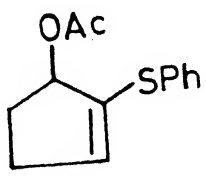
IR spectrum (neat) ν_{max}: 1670 (>C = O) cm^{-1}

^{1}H NMR spectrum (CCl_4): δ 7.36-7.03 (5H, m, aromatic protons), 6.18 (1H, t, =CH-), 2.5-1.94 (6H, m, allylic and other methylenes).

II.5 Preparation of 1-acetoxy-2-phenylthiocycloalk-2-ene

General procedure: 2-Phenylthiocycloalk-2-enone (1.5 mmol) and $CeCl_3.7H_2O$ (582 mg, 1.56 mmol) were dissolved in MeOH (5 mL) and sodium borohydride (60 mg, 1.56 mmol) was added to it in one portion at 0^oC. After 5-10 min of stirring MeOH was removed under reduced pressure. The residue was taken in ether (25 ml) and 3 ml of satd aq.NH_4Cl solution was added to it. The organic layer was then washed with water (5 ml), brine (5 ml) and dried over anhydrous sodium sulphate. Evaporation of ether gave a crude hydroxy compound which was acetylated using acetic anhydride (1.6 mmol) and pyridine (1.56 mmol) in dry CH_2Cl_2 at room temperature. The reaction mixture was stirred for 5 hr and the crude acetate was worked up with ether (25 ml), water (5 ml) and brine (5 ml). Drying and evaporation of ether layer gave a crude acetate which was purified by column chromatography [eluent, petether: ethyl acetate (95:5)]. The properties of acetoxy compounds are described as follows.

1-Acetoxy-2-phenylthiocyclopent-2-ene: (130)



A colourless thick liquid

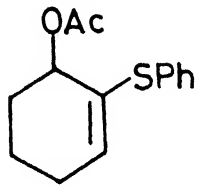
Yield 92%

IR spectrum (neat) ν_{max} : 1725 ($-O-CO-CH_3$) cm^{-1}

^1H NMR spectrum (CCl_4): δ 7.77-7.0 (5H, m, aromatic protons), 5.9-5.73 (1H, t, = CH, J = 3 Hz), 5.73-5.33 (1H, m, -CHOAc), 2.7-1.7 (7H, m, allylic and other methylenes with a methyl singlet of $-O-\overset{\overset{O}{\|}}{C}-CH_3$ at δ 1.87)

Mass spectrum (m/z): 235 $(M+1)^+$, 174 (M^+-CH_3COOH), 65 $(M^+-CH_3COOH-SPh)$.

1-Acetoxy-2-phenylthiocyclohex-2-ene: (131)



A light yellow coloured oil

Yield 95%

IR spectrum (neat) ν_{max} : 1720 ($-O-CO-CH_3$) cm^{-1}

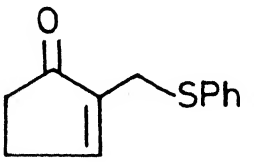
^1H NMR spectrum (CCl_4): δ 7.27 (5H, m, aromatic protons), 6.21 (1H, t, = CH), 5.15 (1H, br. s, -CHOAc), 2.2-1.5 (6H, m, allylic and other methylenes with a methyl singlet of $-O-\overset{\overset{O}{\|}}{C}-CH_3$ at δ 1.8)

Mass spectrum (m/z): 248 (M^+), 249 $(M+1)^+$, 188 (M^+-CH_3COOH) 79 $(M^+-CH_3COOH-SPh)$.

II.6 Preparation of 2-[(phenylthio)methyl] cycloalk-2-ene-1-one[32]

General Procedure: A solution of cycloalkenone (5 mmol), triethylamine (5 mmol), 37% aqueous formaldehyde solution (5 mmol) and thiophenol (5 mmol) in absolute ethanol (15 ml) was refluxed for 24 hr. The cooled solution was concentrated and the residue was partitioned between ether and water. Aqueous layer was extracted with ether (2 x 15 ml) and the combined etherial extracts were washed with 5% aqueous NaOH (10 ml), water (2 x 10 ml) and brine (10 ml). The organic layer was dried over anhydrous Na_2SO_4 and the crude product obtained after removal of ether was purified by column chromatography [eluent: petroleum ether (60-80°C): ethyl acetate 97:3]. The characteristics of these compounds are given below.

2-[(Phenylthio)methyl] cyclopent-2-enone: (128)



Yield 70%

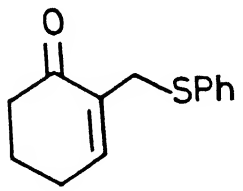
A freely moving liquid

IR spectrum (neat) ν_{max} : 1690, 1620 and 1570 (>C=O, >C=C< and aromatic ring) cm^{-1}

^1H NMR spectrum (CCl_4): δ 7.5-7 (6H, m, =CH- and aromatic protons), 3.73-3.4 (2H, d, $-CH_2SPh$, J = 2 Hz), 2.73-2.13 (4H, m, allylic and other methylenes)

Mass spectrum (m/z): 204 (M^+), 205 $(M+1)^+$, 110, 95

2-[Phenylthio(methyl)]-2-cyclohexenone: (129)



Yield 63%

A clear liquid

IR spectrum (neat) ν_{max} : 1680, 1580 (>C=O, >C=C<) cm^{-1}

^1H NMR spectrum (CCl_4) : δ 7.4-6.9 (5H, m, aromatic protons),

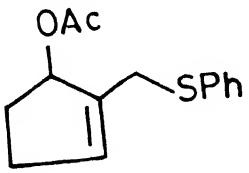
6.65 (1H, m, >C=CH-), 3.57 (2H, br. s, PhS-CH_2-),

Mass spectrum (m/z): 218 (M^+), 219 $(M+1)^+$, 110, 109.

II.7 Preparation of 1-acetoxy-2[(phenylthio)methyl] cycloalk-2-ene

Reduction followed by acetylation was performed as per the procedure as described in sec. II.5.

1-Acetoxy-2[(phenylthio)methyl] cyclopent-2-ene: (134)



Yield 78%

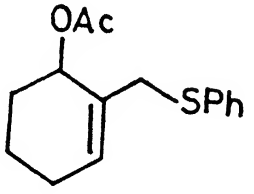
A thick liquid

IR spectrum (neat) ν_{max}: 1720 ($-O-COCH_3$) cm^{-1}

^1H NMR spectrum (CCl_4): δ 7.3-6.93 (5H, m, aromatic protons), 5.87-5.5 (2H, m, -CHOAc and =CH-), 3.5 (2H, d, $-CH_2SPh$, J = 3 Hz), 2.5-1.3 (7H, m, allylic and other methylenes with a methyl singlet due to $-O-COCH_3$ group at about δ 1.93

Mass spectrum (m/z): 248 (M^+), 249 $(M+1)^+$, 205, 189 $[(M+1)^+ - CH_3COOH]$.

1-Acetoxy-2[(phenylthio)methyl] cyclohex-2-ene: (135)



Yield 95%

A clear oil

IR spectrum (neat) ν_{max}: 1710, 1570 (>C=O, >C=C<) cm^{-1}

^1H NMR spectrum (CCl_4): δ 7.33-6.97 (5H, br. s, aromatic protons), 5.77-5.53 (1H, br. t, =CH-), 5.47-5.17 (1H, m, -CHOAc), 3.37 (2H, s, $-CH_2-SPh$), 2.1-1.47 (9H, m, allylic and other methylenes with a methyl ($-O-COCH_3$) singlet at δ 1.92

Mass spectrum (m/z): 262 (M^+), 263 $(M+1)^+$, 202 (M^+-CH_3COOH).

II.8 PLAP Catalysed Hydrolysis of Racemic Acetates

The procedure used for the PLAP hydrolysis is same as describe in sec.I.20.

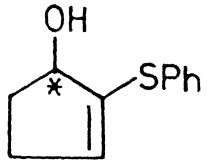
PLAP catalysed hydrolysis of (±) 130

Hydrolysis of racemic (±) **130** (500 mg, 2.136 mmol) with PLAP (600 mg) afforded alcohol (+) **132** and unhydrolysed (-) acetate.

Reaction time: 80 hr

Yield of (+) alcohol : 110 mg (54%)

Compound (132)



A yellow thick liquid

IR spectrum (neat) ν_{max} : 3540, 1600, 1580 (-O-H, >C=C<, aromatic) cm^{-1}

^1H NMR spectrum (CCl_4): δ 7.4-7.06 (5H, m, aromatic protons), 5.7 (1H, br t, = CH), 4.59-4.32 (1H, br m, -CHOH), 2.9-1.66 (5H, m, -OH, allylic and other methylenes).

$[\alpha]^{25}_D$: (+) 46.279 (C1, $CHCl_3$)

e.e : 96%

Yield of the recovered acetate : 270 mg

$[\alpha]^{25}_D$: (-) 17.475 (C1, $CHCl_3$)

e.e : 53%

The (-) acetate has its IR, ^1H NMR data identical with that of the corresponding racemic compound.

PLAP catalysed hydrolysis of (±) (131)

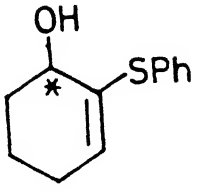
Hydrolysis of racemic (±) **131** (400 mg, 1.61 mmol) with PLAP (480

mg) afforded alcohol (+) **133** and unhydrolysed acetate (-) **131**.

Reaction time : 85 hr.

Yield of (+) alcohol: 128 mg (77%)

Compound (133)



A yellow oil.

IR spectrum (neat) ν_{max}: 3560, 1620, 1580 (-OH, >C=C<, aromatic) cm^{-1}

^1H NMR spectrum (CCl_4): δ 7.29-6.95 (5H, m, aromatic protons), 6.03 (1H, t, = CH, J = 6 Hz), 3.85 (1H, br s, -CHOH), 2.5-1.3 (7H, m, -OH, allylic and other methylenes).

$[\alpha]_D^{25}$: (+) 93.750 (C1, $CHCl_3$)

e.e : 81%

Yield of the recovered acetate : 218 mg

$[\alpha]_D^{25}$: (-) 58.733 (C1, $CHCl_3$)

e.e : 34%

The (-) acetate has its IR, ^1H NMR data identical with that of the corresponding racemic compound.

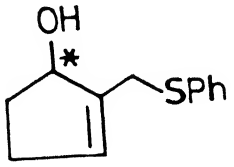
PLAP catalysed hydrolysis of (±) (134)

Hydrolysis of racemic (±) **134** (189 mg, 0.76 mmol) with PLAP (226 mg) afforded alcohol (+) **136** and unhydrolysed acetate (-) **134**.

Reaction time : 70 hr

Yield of the alcohol : 26 mg (34%)

Compound (136)



A pale yellow oil.

IR spectrum (neat) ν_{max}: 3550, 1610, 1575 (-OH, >C=C<, aromatic) cm^{-1}

^1H NMR spectrum (CCl_4): δ 7.3-6.97 (5H, m, aromatic protons), 5.51 (1H, br s, = CH), 4.85-4.95 (1H, m, -CHOH), 3.52 (2H, br s, CH_2SPh), 2.6-1.5 (5H, m, -OH, allylic and other methylenes)

$[\alpha]^{25}_D$: (+) 18.226 (C1, $CHCl_3$)

e.e : 74%

Yield of the recovered acetate : 95 mg

$[\alpha]^{25}_D$: (-) 8.428 (C1, $CHCl_3$)

e.e : 30%

The acetate (-) **134** acetate has its IR, ^1H NMR data identical with that of the corresponding racemic compound.

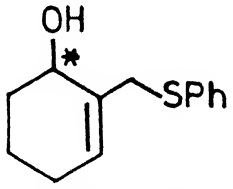
PLAP catalysed hydrolysis of (±) (135)

Hydrolysis of racemic (±) **135** (524 mg, 2 mmol) with PLAP (626 mg) afforded alcohol (+) **137** and unhydrolysed acetate (-) **135**.

Reaction time : 72 hr

Yield of the alcohol : 174 mg (79%)

Compound (+)(137)



A viscous liquid

IR spectrum (neat) ν_{max}: 3560, 1615, 1580 (OH, >C=C<, aromatic) cm^{-1}

^1H NMR (CCl_4): δ 7.25-6.9 (5H, m, aromatic protons), 5.35 (1H, s, = CH), 4.15 (1H, br s, -CHOH), 3.39 (2H, br s, $-CH_2SPh$), 2.3-1.3 (7H, m, -OH, allylic and other protons).

$[\alpha]^{25}_D$: (+) 26.017 (C1, $CHCl_3$)

e.e : 75%

Yield of the recovered acetate : 230 mg

$[\alpha]^{25}_D$: (-) 15.091 (C1, $CHCl_3$)

e.e : 40%

The acetate (-) **135** has its IR, ^1H NMR data identical with that of the corresponding racemic compound.

II.9 Determination of enantiomeric purity of (+) alcohol

Mosher's ester of alcohols were prepared following the same procedure as given in Sec. I.21.

The properties of the Mosher's esters are the following

Mosher's ester of (+)(132)

A clear liquid

^1H NMR spectrum ($CDCl_3$): The ^1H NMR spectrum of this compound contains two singlets at δ 3.63 and δ 3.59 with a intensity ratio of 1.96: 0.04 which shows the enantiomeric purity of (+) **132** to be 96%

Mosher's ester of (+)(133)

A pale yellow liquid

^1H NMR spectrum ($CDCl_3$): The ^1H NMR spectrum of this compound contains two singlets at δ 3.64 and δ 3.56 with a intensity ratio 4.58:0.5 which establishes the enantiomeric purity of (+) **133** to be 80%.

Mosher's ester of (+)(136)

A colourless liquid

^1H NMR spectrum ($CDCl_3$): The ^1H NMR spectrum of this compound contains two singlets at δ 2.24 and δ 2.22 in the ratio 5: 0.75 establishing the enantiomeric purity of (+) **136** to be 74%.

Mosher's ester (+)(137)

A yellow coloured liquid

^1H NMR spectrum ($CDCl_3$): The ^1H NMR of this compound showed two singlets at δ3.6 and δ 3.53 in the ratio 1:0.14 establishing the enantiomeric purity of (+) **137** to be 75%.

II.10 Determination of enantiomeric excess of unhydrolysed (-) acetates

The ^1H NMR (400 MHz) spectra of acetates (5 mg) were recorded in the presence of (+) $Eu(hfc)_3$ (20 mg).

The characteristics of spectra are explained below

Compound (-)(130)

The ^1H NMR spectrum of (-) **130** (5 mg) having two distinct singlets atδ2.122 andδ2.092 due to methyl protons of ($-O-COCH_3$) with an intensity ratio of 1.15:0.35 shows that the optical purity of the chiral acetate is 53%.

Compound (-) (131)

The ^1H NMR spectrum of (-) **131** (5 mg) with two singlets at δ 3.34 and δ 3.165 due to the methyl protons of ($-O-COCH_3$) with an intensity ratio of 2.03:1 shows that the optical purity of the unhydrolysed acetate is 34%

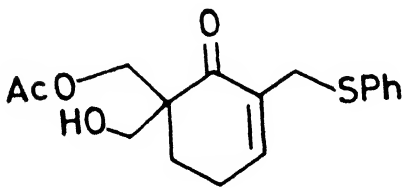
Compound (-) (134)

The ^1H NMR spectrum of (-) **134** (5 mg) with two singlets at δ 3.74 and δ 3.7 due to the methyl protons of ($-O-COCH_3$) with an intensity ratio of 1.857:1 shows that the enantiomeric purity of this compound is 30%.

Compound (-) (135)

The ^1H NMR spectrum of (-) **135** (5 mg) with two singlets at δ 2.25 and δ 2.08 due to the methyl protons of ($-O-COCH_3$) with an intensity ratio of 2.33:1 shows that the enantiomeric purity of the compound is 40%

II.11 Synthesis of compound (139A)



During the preparation of compound **129** (cf. sec II.6), excess of formaldehyde was added and the refluxing was continued for additional 24 hrs. Usual work up (cf. II.6) gave a crude product whose purification resulted into a compound, presumably the diol **138** which was acetylated using acetic anhydride, pyridine, DMAP.

The crude product obtained was purified by column chromatography (eluent: petroleum ether and ethyl acetate 97:3).

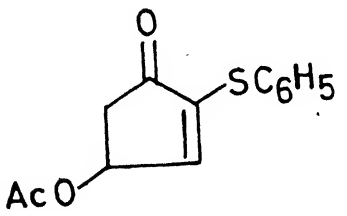
Yield 52%

IR spectrum (neat) ν_{max}: 1720 (>C = O), 1570 (>C = C<) cm^{-1}

^1H NMR spectrum (CCl_4): δ 7.4-6.83 (5H, m, aromatic protons), 6.6 (1H, br. t, >C = CH-) 4.17 (2H, s, $-CH_2OAc$), 3.6 (2H, s, $-CH_2-SPh$), 3.13 (2H, s, $-CH_2OH$), 2.5-1.83 (8H, m, -OH, allylic and other methylenes and with a methyl singlet of $-O-COCH_3$ at δ 1.93.

Mass spectrum (m/z): 320 (M^+), 302 (M^+-H_2O).

II.12 Preparation of 4-acetoxy-2-phenylthiocyclopent-2-enone:(141)



A mixture of compound **126** (1 g, 5.2 mmol), NBS (1.125 gm, 6.3 mmol) and AIBN (100 mg) were taken in CCl_4 (10 ml) and the reaction mixture was refluxed for 2.5 hr. The reaction mixture was then cooled by keeping the reaction flask in the freezer for 1/2 an hr. The solid residue was filtered and washed thoroughy with cold CCl_4 (10 ml). The filtrate was then worked up with water (2 x 5 ml) , 10% sodium thiosulphate (5 ml) and brine (5 ml). The organic layer was dried over anhydrous Na_2SO_4 and CCl_4 removed under reduced pressure (water bath temperature 45°C) to get crude bromoenone **140** (Fig. 24). The crude product itself

was used for the next reaction which was treated with acetic acid (17 ml) and AgOAc (0.97 gm, 5.80 mmol). The resultant mixture was stirred at room temperature for 12 hr. Precipitated AgBr was filtered and acetic acid removed under reduced pressure. The crude product was purified by column chromatography (eluent: pet. ether (60-80°C): ethyl acetate = 92:8).

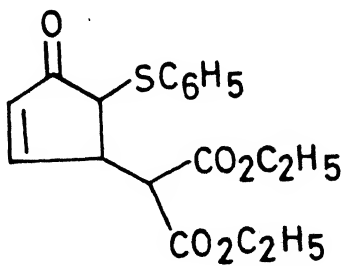
Yield : 59%

IR spectrum (neat) ν_{max}: 1720, 1740 (>C = O, -O-$COCH_3$) cm^{-1}

^1H NMR spectrum (CCl_4): δ 7.32 (5H, m, aromatic protons), 6.27 (1H, d, = CH-, J = 3 Hz), 5.5 (1H, m, $-CH_d(OAc)$), 2.9 (1H, d.d, $-\overset{H_c}{\underset{H_b}{C}}-CH_d(OAc)$, J = 16 Hz, 9 Hz), 2.26 (1H, d.d, $-\overset{H_c}{\underset{H_b}{C}}-CH_d(OAc)$, J = 16 Hz, J = 3 Hz), 1.93 (3H, s, -O-$COCH_3$)

Mass spectrum (m/z): 248 (M^+), 206 ($M^+ - CH_2=C=O$), 189 ($M^+ - CH_3COOH$)

II.13 Preparation of 3-(α,α'-dicarboethoxymethyl)-2-phenylthio-cyclopent-4-enone (142)



Compound **141** (1 mmol) was dissolved in 5 ml of DME and to it was added a mixture of diethyl malonate (1 mmol) and potasium-t-butoxide (1 mmol). The reaction mixture was stirred at room temperature for 7 hr and then worked up with ether (2x 10 ml), water (5 ml) and brine (5 ml). Ether was removed and the crude

product so obtained was purified by column chromatography (eluent: pet ether 60-80°C : ethyl acetate = 90:10).

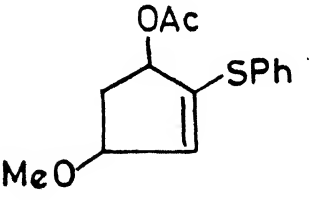
Yield 55%

IR spectrum (neat) ν_{max}: 1730 (>C = O)

^{1}H NMR spectrum (CCl_4): δ 7.67-6.6 (6H, m, aromatic protons and -C-CH=CH-), 6.07 (1H, d.d, -C-CH=CH-, J = 2 Hz, 6 Hz), 4.13 (4H, 2q, $-OCH_2-CH_3$, J = 7 Hz), 3.6-3.13 (3H, m, >CHSPh, $-CH(CO_2C_2H_5)_2$ and allylic methine), 1.23 (6H, 2t, $-OCH_2CH_3$, J = 7 Hz)

Mass spectrum (m/z): 348 (M^+), 274 ($M^+-C_2H_5COOH$), 188 ($M^+-CH_2(CO_2Et)_2$)

II.14 Synthesis of 1-acetoxy-4-methoxy-2-phenylthiocyclopent-2-ene: (147)



Compound **141** (1 mmol) was reduced with $NaBH_4/CeCl_3.7H_2O$ and the crude reduced product was acetylated using acetic anhydride, pyridine, and DMAP following the same procedure as described in Sec. II.5.

Yield 30%

A yellow coloured oil

IR spectrum (neat) ν_{max}: 1720 (>C = O) cm^{-1}

^{1}H NMR spectrum (CCl_4): δ 7.6-7.1 (5H, m, aromatic protons),

5.73-5.2 (3H, m, -CHOAc, = CH-), 4.47-4.1 (1H, m,-CHOMe), 3.13 (3H, s, $-OCH_3$), 3.0-1.75 (5H, m, methylene and methyl singlet of $-O-COCH_3$ at δ1.93)

Mass spectrum (m/z): 232 (M^+).

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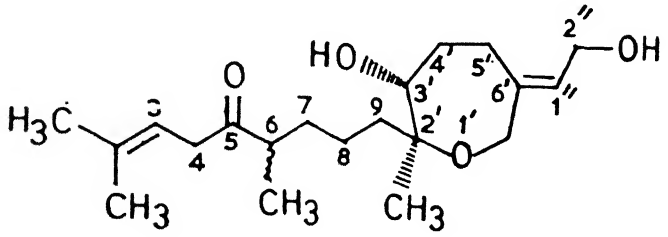
CHAPTER III

RADICAL CYCLISATION APPROACH TOWARDS THE SYNTHESIS OF ZOAPATANOL

INTRODUCTION

III.1 The diterpene zoapatanol **1** isolated from the Mexican zoapatle plant[1] (Monatanoa tomentosa) which has been traditionally used in folk medicine to terminate early pregnancy has generated much interest over the last decade because of its reported antifertility properties[1]. It has also been found to possess unique "uteroevacuant" activity[2]. The structure of zoapatanol was elucidated in 1979 by Levine et al[1]



1 Zoapatanol

Figure 1

The structure has been further confirmed[3] by X-ray analysis. Zoapatanol is having an oxepane ring and the 2' and 3' position of the ring is asymmetrically substituted. The stereochemistry at C_2 and C_3 is S and R respectively. The geometry of the hydroxy ethylidine group has been assigned as 6'E configuration. The 6-methyl group adjacent to the carbonyl group is not defined stereochemically.

Due to the potential of zoapatanol for use in human contraception and the novelty of its unique molecular structure interest among chemists is generated towards its stereocontrolled synthesis. Chen and Rowand[4] were the first ones to synthesise

zoapatanol from the epoxy compound **2** which is having a 2-hydroxy ethylidine group at an early stage. They used 2-methyl-6-methylene-(E)-2, 7-octadien-1-ol **3** as a starting material to form **5** (Fig. 2). The cyclisation of **4** with trifluoroacetic acid (TFA) in dichloromethane at $0^{\circ}C$, gave the oxepane ring **5** in a stereospecific fashion. The terminal tetrahydropyran-2-yloxy group was modified to get the desired side chain.

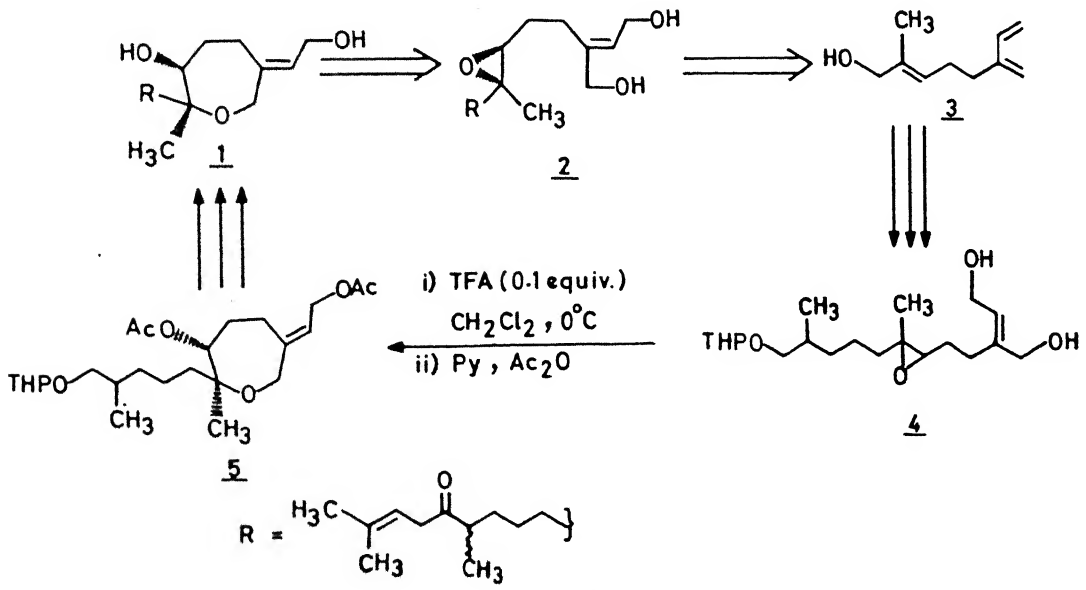


Figure 2

The synthetic strategy of Nicolaou et al[5] is based on the opening of an epoxy ring to get the desired oxepane ring as shown in Fig. 3. The side chain was synthesised from a methoxy enol ether **6**. The methyl group at 2' position of (±) **1** was introduced with the

help of chelation controlled methodology to obtain **11** from **10** by reacting it with 2-equiv MeMgCl at -105°C in THF. Construction of the oxepane ring system **13** was accompanied by intramolecular epoxide opening using $K^{+}CH_2SOCH_3$ in DMSO followed by the cleavage of the resulting diol with $NaIO_4$. This crucial oxepane intermediate was then subsequently transformed into zoapatanol (±) **1** via a series of reactions (Fig. 3).

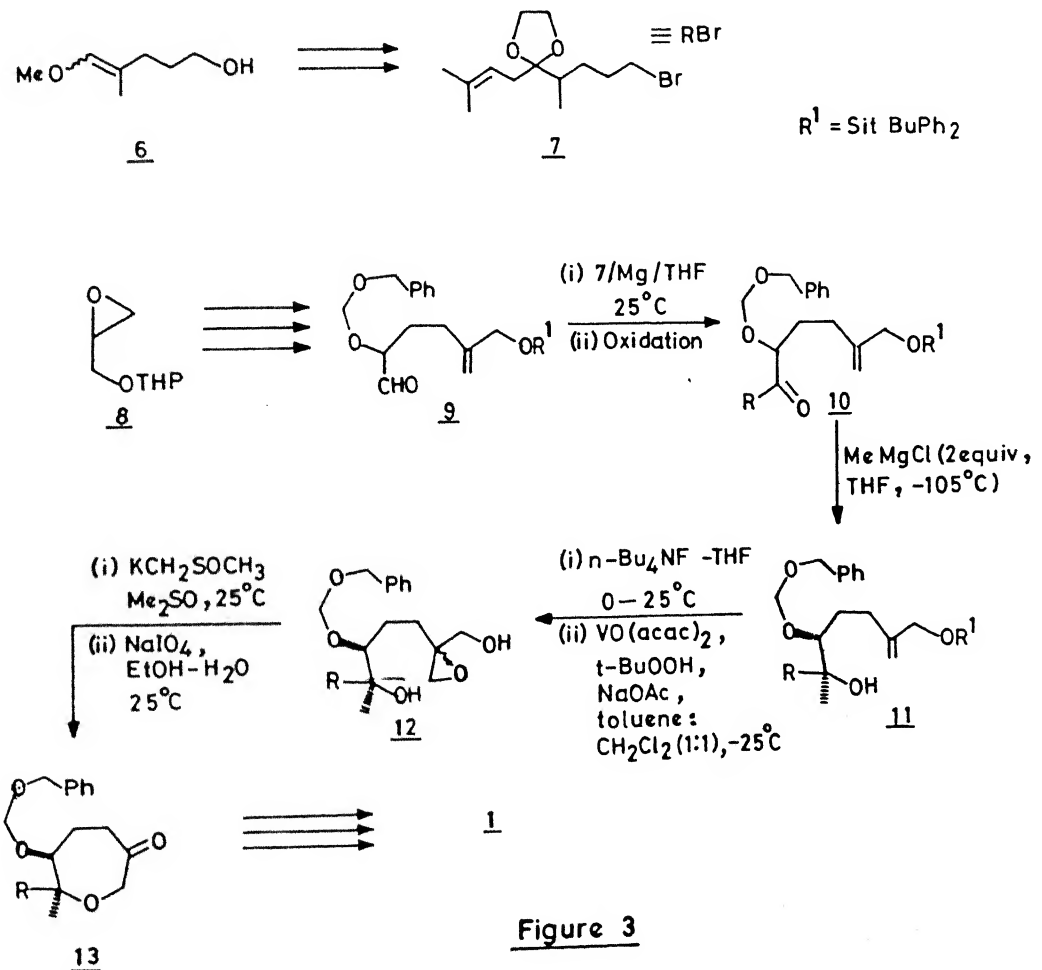


Figure 3

Kane and Doyle[6] have synthsised (±) zoapatanol from a bicyclic intermediate **14** to establish and control the stereorelationship required for the ring vicinal alkyl and hydroxy groups. Construction of the oxepane ring system involved conversion of the ketone **15** to the lactone **16** via its Baeyer-Villiger oxidation. This lactone **16** was transformed into the β-keto ether **17(b)** via a set of reactions involving enol phosphate **17(a)** as shown in Fig. 4. After having constructed the basic oxepane system **17(b)** it was then converted into (±) zoapatanol through a number of simple transformations

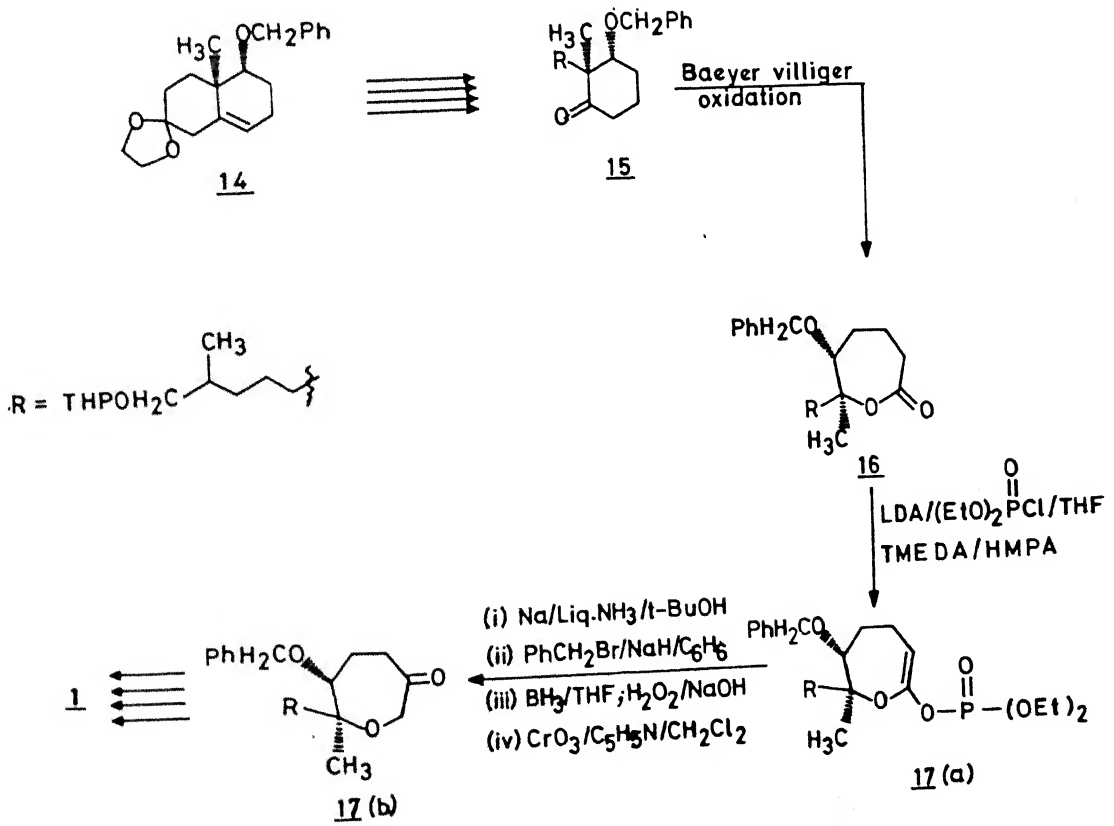


Figure 4

Cookson and Livertone[7a] have used similar epoxy compound **23** (Fig. 5) which Chen and Rowand[4] have used (cf. **23** (hydroxy group was protected as THP ether instead of benzyl ether)) to get the oxepane ring. The key step in this new synthesis of zoapatanol involved stannic chloride catalysed isomerisation of the epoxy diol **23** to an oxepane system in which differential protection of the hydroxy groups allowed oxidation to the acid **24** followed by addition of the prenyl group to complete the side chain. An important step in construction of the intermediate epoxy diol **23** was the zirconium catalysed cis- addition of trimethyl aluminium to the acetylene according to Negishi[7b] and reaction of the 'ate' complex **20** with n-butyllithium with ethylene oxide to form the E alcohol **21**. The homoallylic iodide **22** was a key intermediate to give the epoxy diol **23**.

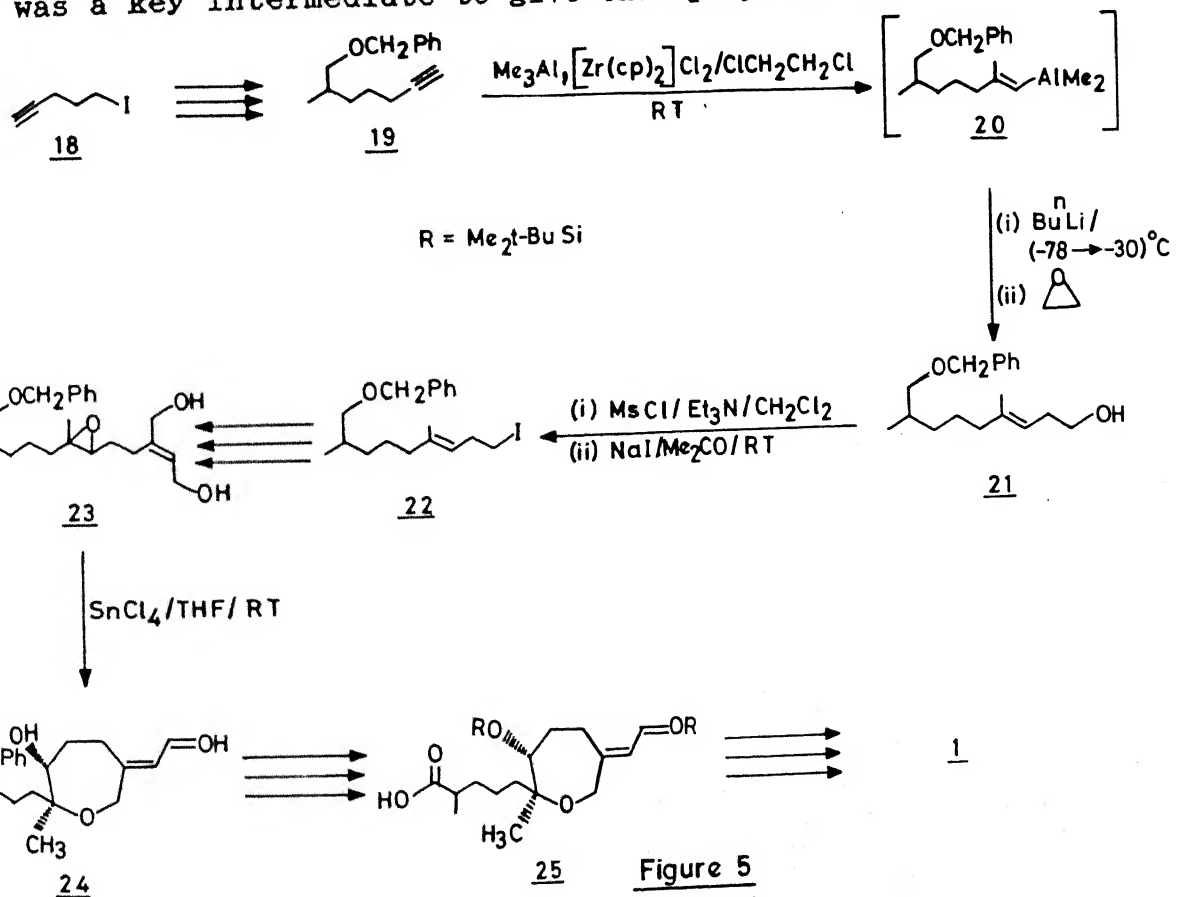


Figure 5

In 1989 a yet another approach by Kociensky et al[8] appeared in the literature which also involved a somewhat similar approach towards the construction of the main oxepane unit as was utilised by Chen and Rowand[4] and Cookson and Liverton[7]. The epoxy diol **31** used in the strategy by Kociensky et al is however slightly different from the previous ones. Further, synthesis of this diol involved a highly stereoselective approach towards constructing the trisubstituted alkene **28** using reaction developed by Wenkert et al[9]. This synthesis is outlined in Fig. 6.

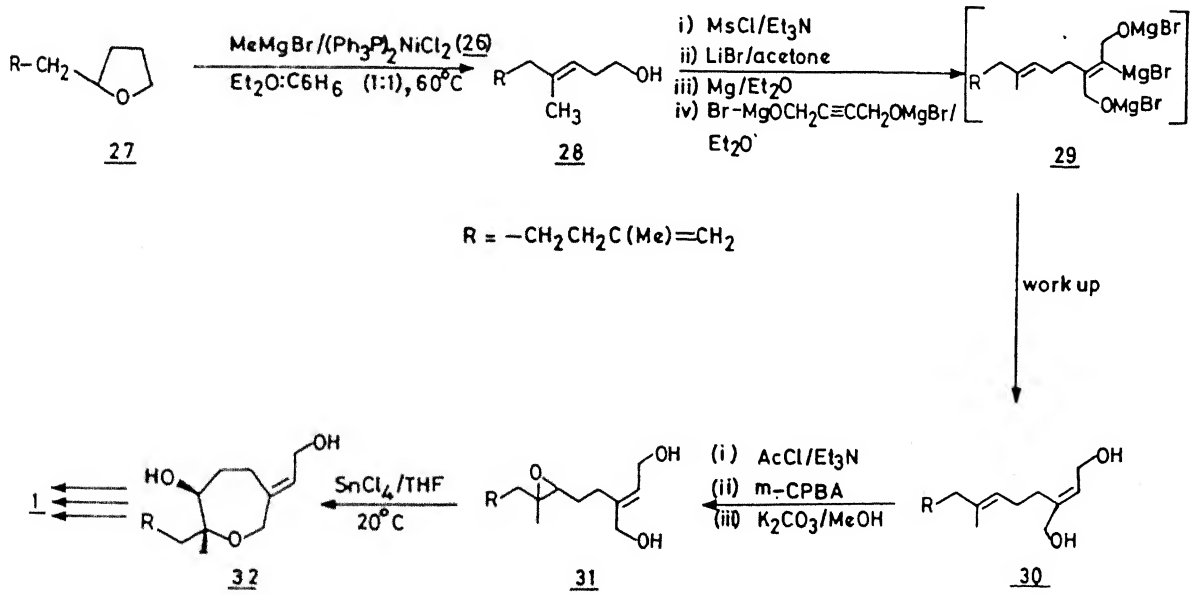


Figure 6

In addition to the above mentioned syntheses, Moody et al[10] have recently reported an interesting approach towards the synthesis of oxepane derivatives related to zoapatanol. This involved rhodium carbenoid mediated cyclisation of ω-hydroxy- α-diazo-β-keto esters. Synthesis of one such intermediate viz. **38** is delineated in Fig. 7.

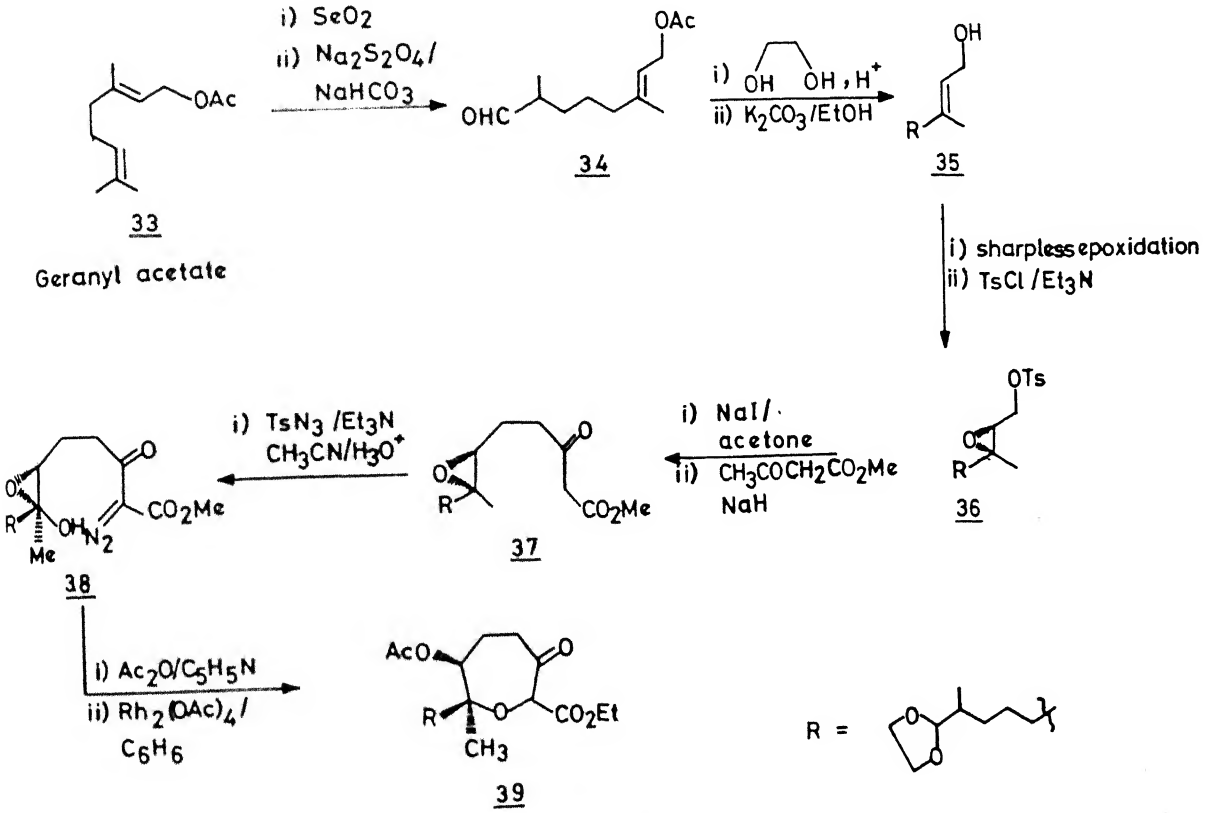
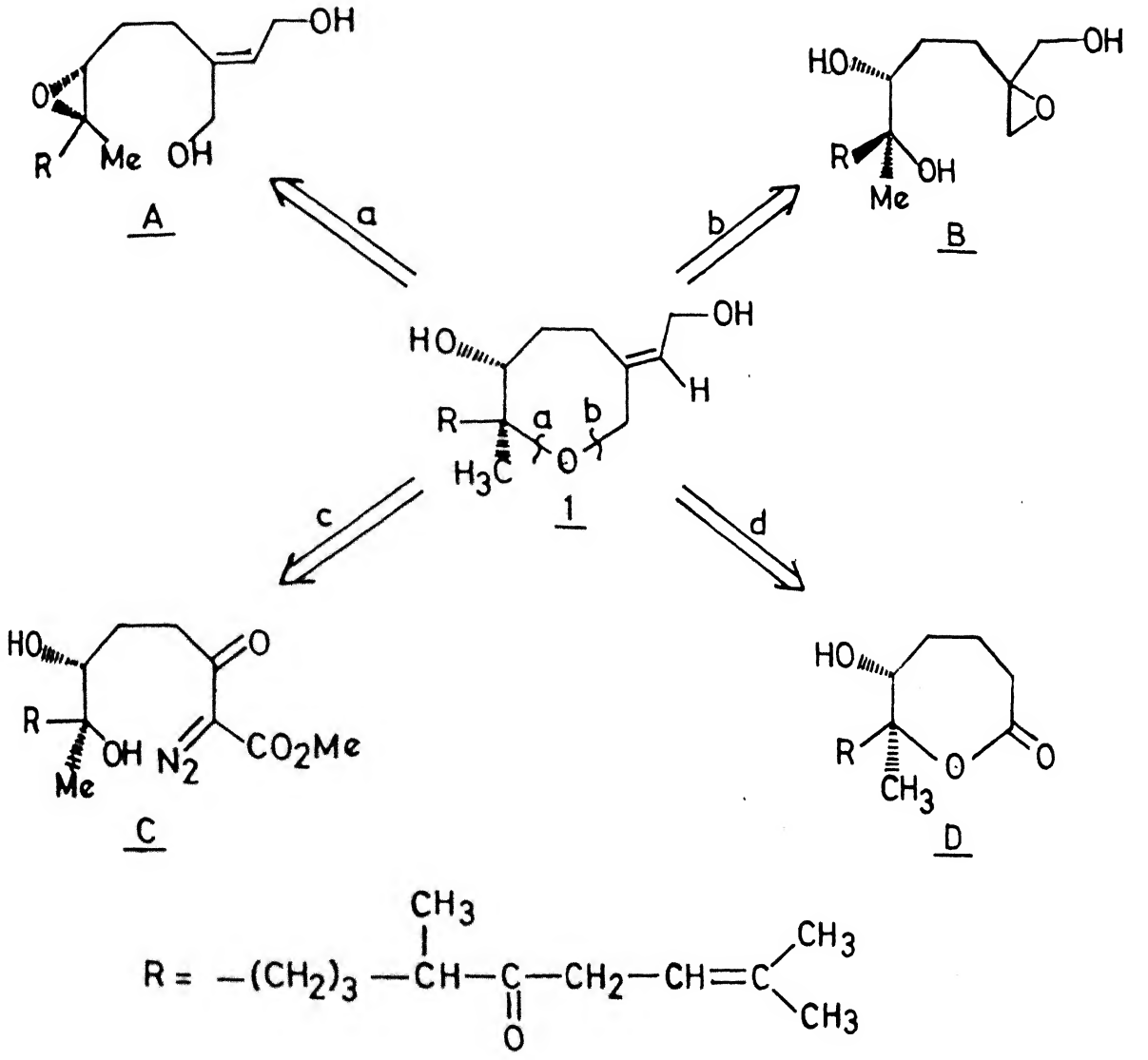


Figure 7.

III.2 Results and Discussion

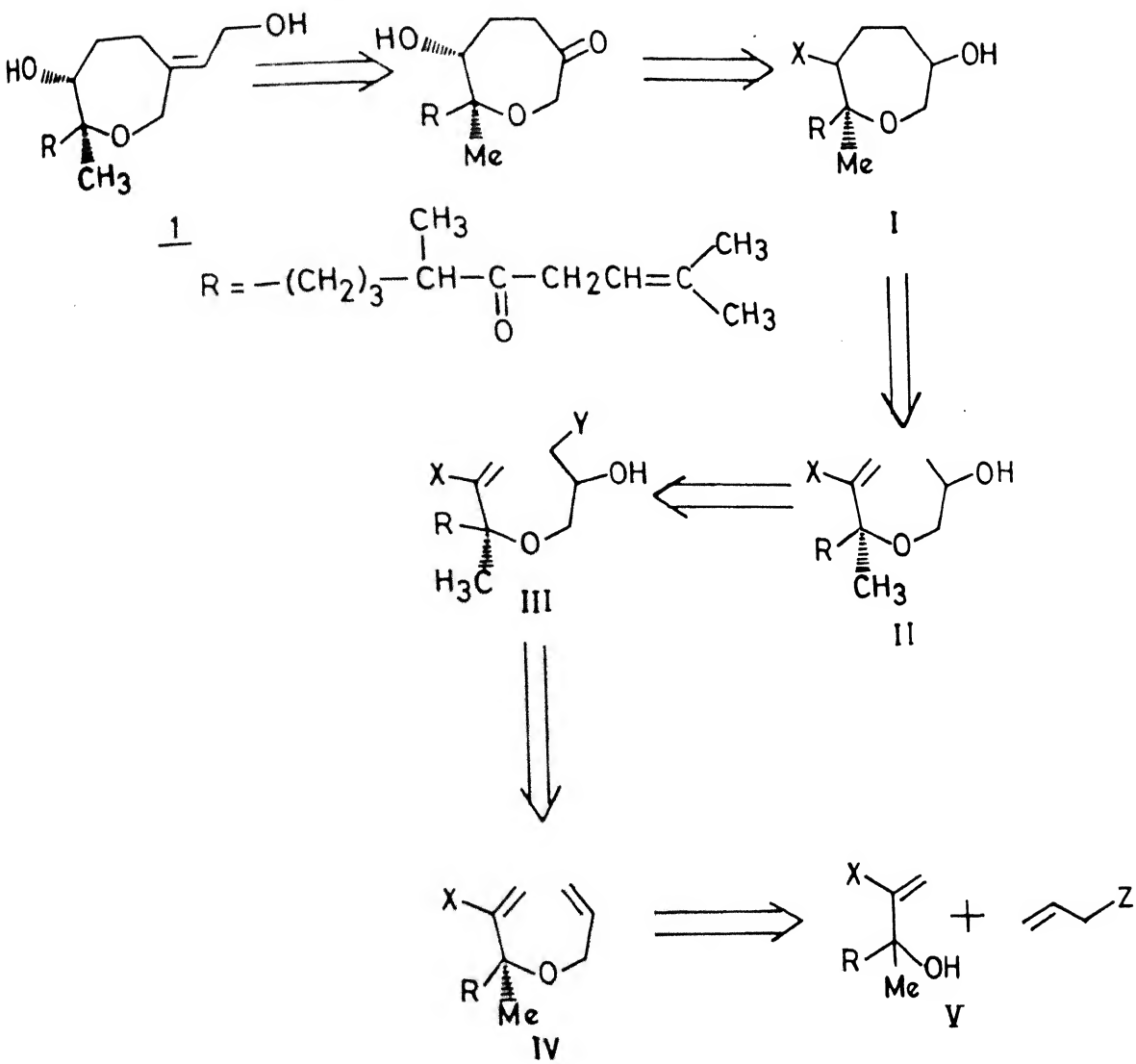
The introduction part of this chapter deals with various synthetic endeavours towards the synthesis of zoapatanol (±) **1** described in the literature. These approaches towards the oxepane ring systems basically are of two types viz. (i) starting from cyclic precursors and (ii) elaboration of a cyclic structure. Towards the first approach the crucial precursors are of the type A and B as shown in Fig. 8 via the cleavage of bonds a and b. Compounds of type A lead to oxepane ring system via intramolecular epoxide ring opening under acidic condition[4,7a,8]. Whereas the B type structure undergoes intramolecular epoxide ring opening under basic condition[5]. A yet another approach[10] towards the oxepane system involving bond 'b' cleavage involves the cyclisation of 'c'. In the second approach lactone of type 'D', obtained[6] via Baeyer- Villiger oxidation of the corresponding cyclic ketone, is utilised for zoapatanol[6] synthesis.

A close scrutiny of the structure of zoapatanol suggests that other than the above mentioned approaches possibilities of C-C bond formation from an appropriately substituted acyclic precursor do exist. Of several such possibilities the one which we have considered involves a radical induced intramolecular C-C bond formation. Retrosynthetic analysis of zoapatanol which supports our approach is shown in Fig. 9.



$$R = -(CH_2)_3-\underset{\displaystyle CH_3}{\underset{|}{CH}}-\underset{\displaystyle O}{\overset{\displaystyle \|}{C}}-CH_2-CH=\overset{\displaystyle CH_3}{\overset{|}{C}}-CH_3$$

Figure 8



Retrosynthesis

Figure 9

This radical cyclisation approach as depicted in Fig. 9 involves an allowed 7-endo trig mode according to Baldwin's rule[11]. In order to test the validity of this approach a model study has been carried out. Literature survey revealed that structures of type V (Fig. 9) are readily available via Baylis-Hillman[12] reaction. One of the simplest compounds **40**(Fig. 11) available via this reaction was chosen by us for the present study. This was obtained by the reaction of acrylonitrile with

benzaldehyde in the presence of 1,4-diazabicyclo (2.2.2) octane (DABCO) according to a literature procedure[13]. Compound **40** was then reacted with allylbromide to form **41** in 61% yield. This compound represented structure IV of Fig. 9 for model study. Here X is not a direct precursor of an OH group and R does not correspond to the side chain of the zoapatanol. At the same time methyl group is also not present. However, preliminary studies towards the construction of the oxepane ring system pertaining to zoapatanol where substituents are at proper positions have been attempted using compound **41** (Fig.11). Structure of compound **41** was confirmed on the basis of its spectral data (cf. III.3.2) section. In order to convert this compound into the precursor of type III (Fig. 9) initial studies were carried out using oxymercuration reaction[14] on compound **41** to obtain oxymercurials **42**. The reductive coupling of these mercurials

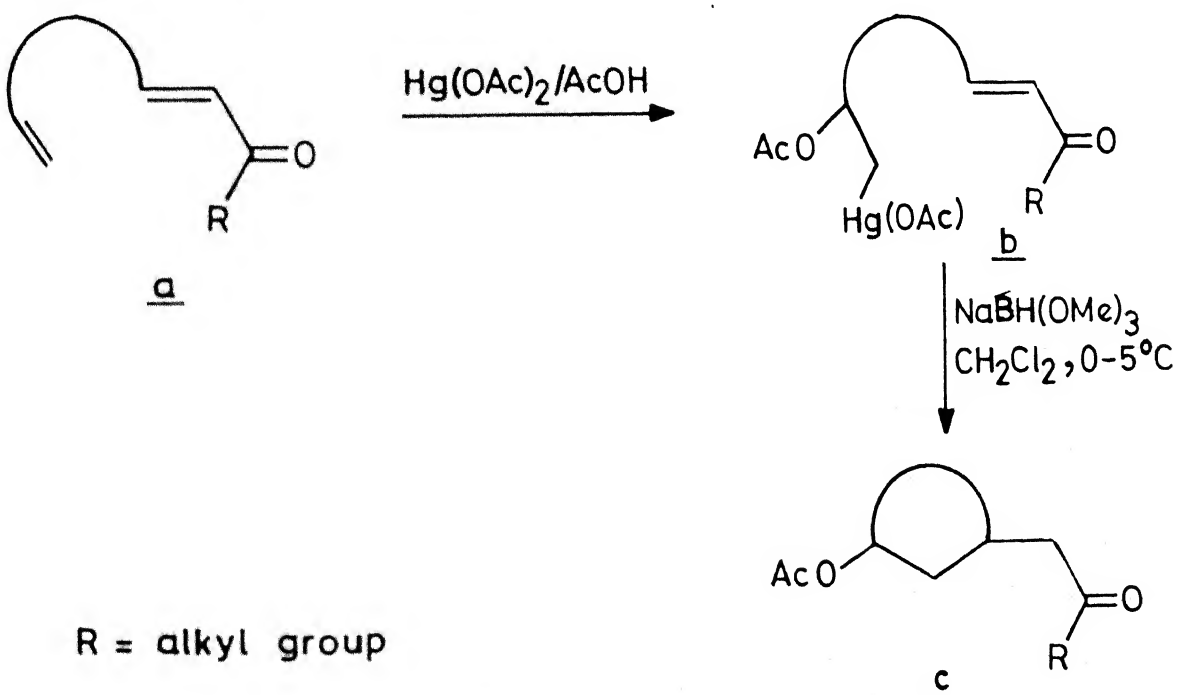


Figure 10

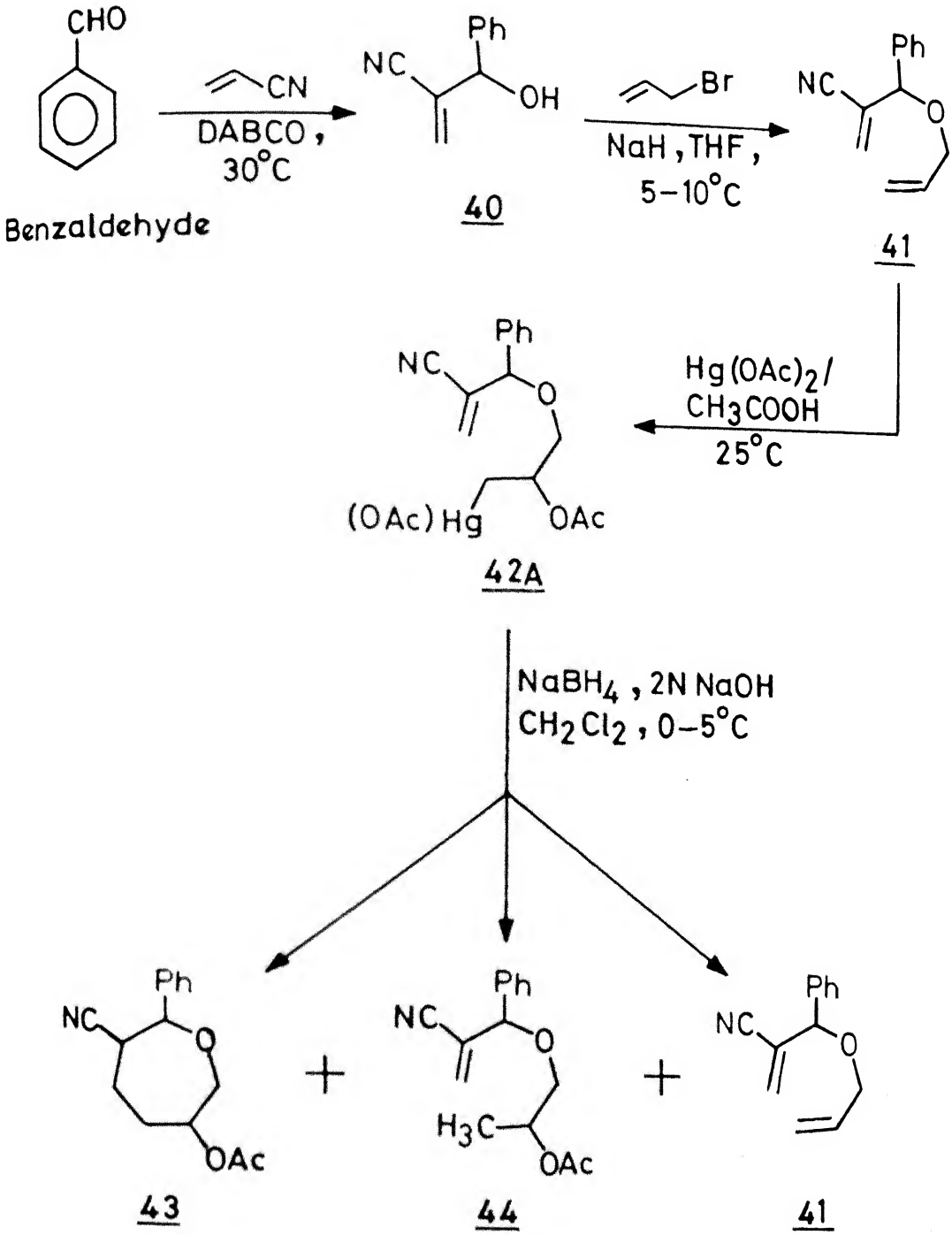

CHO
Benzaldehyde
CN
DABCO,
30°C
Ph
NC
OH
40
Br
NaH, THF,
5–10°C
Ph
NC
O
41
Hg(OAc)2/
CH3COOH
25°C
Ph
NC
O
(OAc)Hg
OAc
42A
NaBH4, 2N NaOH
CH2Cl2, 0–5°C
Ph
NC
O
OAc
43
+
Ph
NC
O
H3C
OAc
44
+
Ph
NC
O
41

Figure 11

were expected to lead to the oxepane system based on literature precedence[15,16] for both inter as well as intramolecular C-C bond formation. The report by Danieshefsky[16] is especially interesting as it deals with the intramolecular cyclisation via 5-exo and 6-exo trig modes as shown in Fig. 10. In the present study formation of the oxepane system via 7-endo trig mode of cyclisation was therefore expected. Oxymercuration of **41** was carried out under two different conditions viz. with acetic acid and with methanol. The acetoxy mercurial **42A** was reduced under basic conditions with $NaBH_4$ according to the literature procedure[17]. It gave two products, **43** and **44** along with some amount of the starting material in 9%, 15% and 68% yield respectively (Fig. 11). Structures of these products were confirmed by spectral and analytical means. Compound **43** showed in its IR spectrum strong peaks at 2218 cm^{-1} and at 1740 cm^{-1} corresponding to the -CN group and the acetate group respectively. In its ^1H NMR spectrum signals at δ 0.8 - 1.8 (4H, m, $2CH_2$s), 1.93-2.1 (3H, 2s, O-CO-CH_3), 2.66-3.23 (1H, m, -CHCN), 3.26-4.33 (4H, m, -CHOAc, -O-CHPh , -O-CH_2 with a doublet centering at δ 4.2, J = 7 Hz), 7.16 (5H, br.s, aromatic protons) were observed. The doublet at δ 4.2 corresponds to the benzylic methine and since the J value is only 7 Hz the relationship between the proton e and d must be cis. The presence of two singlets for O-CO-CH_3 at δ 1.93, 2.1 indicates that this product is a mixture of two stereoisomers **43A** and **43B** in a ratio of 3:2 as indicated by the integration of these two singlets (Fig. 12).

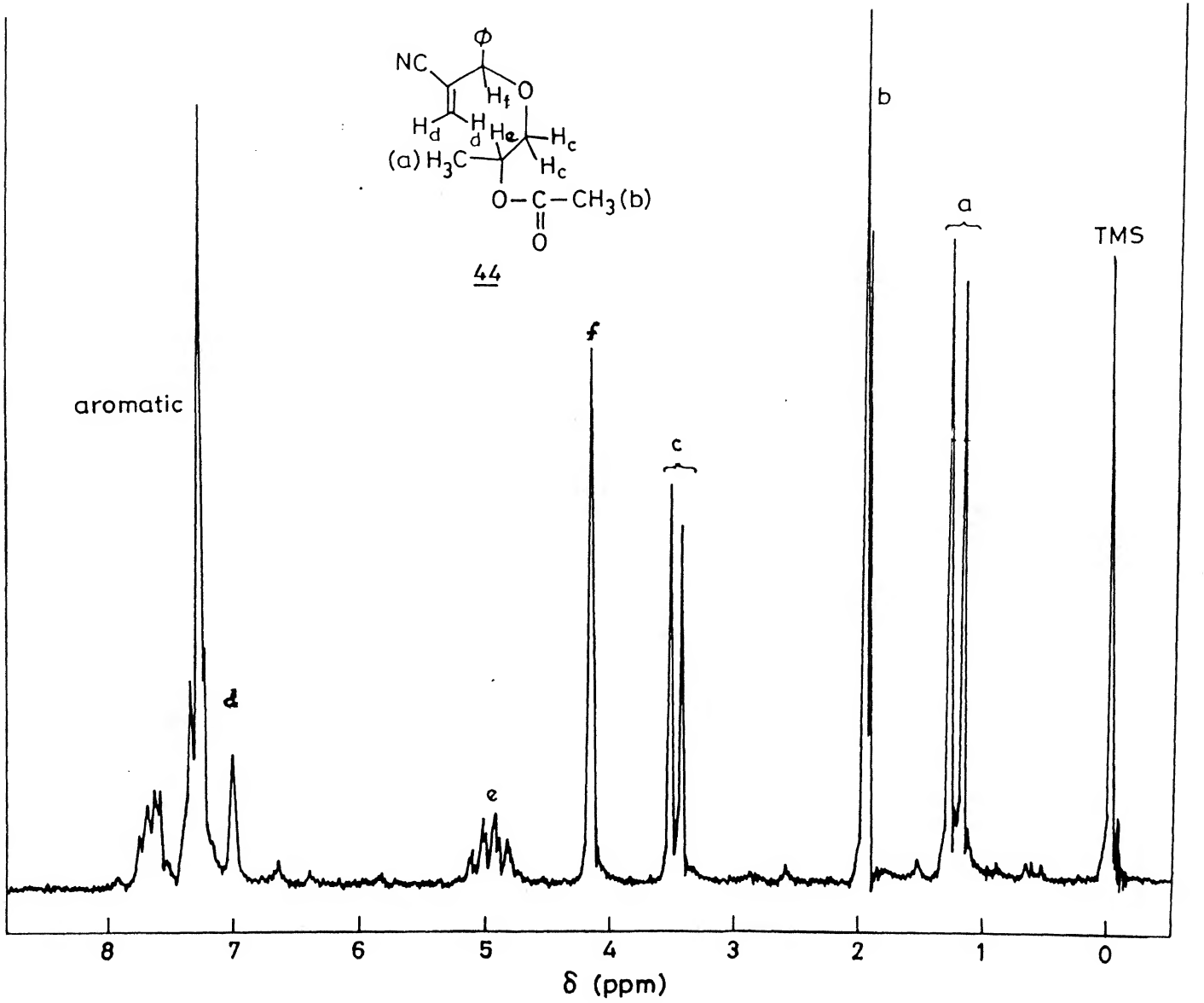
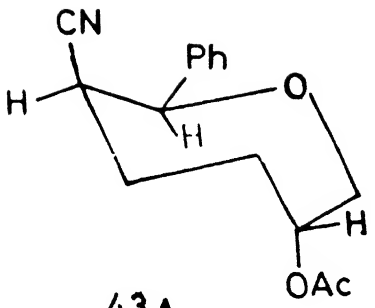
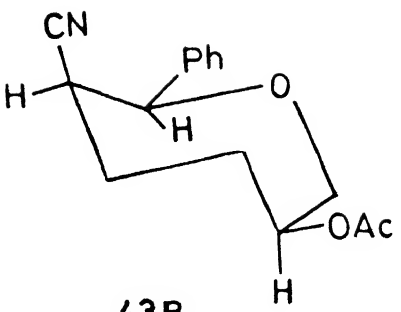


Figure III.2: ^1H NMR spectrum (60 MHz) of **44**



43A



43B

Figure 12

Structure of compound **44**, which is formed by mere reduction of the C-Hg bond, was consistent with the spectral data assigned to it. In its IR spectrum strong peaks at 2208 ($\nu_{C\equiv N}$) and 1730 ($\nu_{O-CO-CH_3}$) cm^{-1} were observed. The ^1H NMR spectrum showed peaks at δ 1.23 (3H, d, $-CH-CH_3$, J = 6 Hz), 1.9-1.94 (3H, 2s, $-O-CO-CH_3$), 3.47 (2H, d, $-OCH_2$, J = 5 Hz), 4.13 (1H,s,(Ph)-CH-O-), 4.93 (1H, sextet, -CH (OAc) (CH_3)), 6.19-7.77 (7H, m, aromatic and = CH_2 protons). Mass spectral analysis showed M^+ peak at m/z at 259. Appearance of two singlets at δ 1.9 and 1.94 is due to the presence of four possible diastereomers. It is however difficult to predict the ratios of these diastereomers on the basis of the analysis of low resolution (60 MHz) ^1H NMR spectrum, although the two peaks are of unequal intensity. In order to improve the yield of the cyclised product **43** the reaction was also carried out in aqueous THF as reported by Brown and Geoghegan[18]. However this did not improve the yield of the

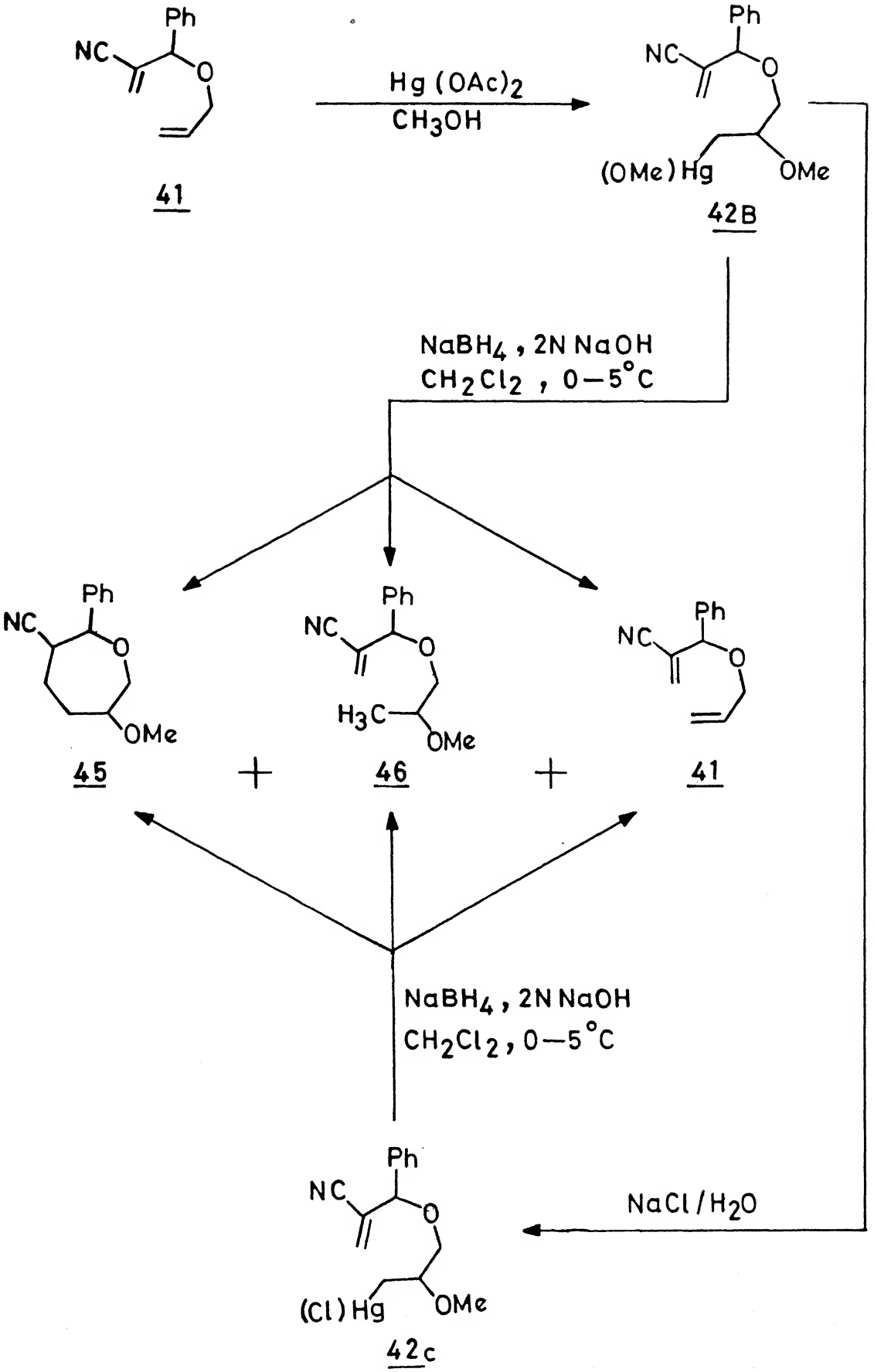

Ph
NC
O
41
Hg (OAc)2
CH3OH
Ph
NC
O
(OMe) Hg
OMe
42B
NaBH4 , 2N NaOH
CH2Cl2 , 0—5°C
Ph
NC
O
OMe
45
+
Ph
NC
O
H3C
OMe
46
+
Ph
NC
O
41
NaBH4 , 2N NaOH
CH2Cl2 , 0—5°C
Ph
NC
O
(Cl) Hg
OMe
42c
NaCl / H2O

Figure 13

cyclised product. It is possible that use of $Na(OMe)_3BH$[16] in place of $NaBH_4$ might be more useful to obtain high yield of the cyclised product. We have, however, not carried out this reaction in the present study.

Methoxymercuration of **41** followed by reduction with $NaBH_4$ was also carried out in order to find out the effect of -OMe group versus $-O-CO-CH_3$ group towards the product distribution. Thus reaction of **41** with mercuric acetate in methanol was carried out in an analogous manner as acetoxymercuration. Reduction of the crude product with $NaBH_4$ under basic condition was then performed. However, this reaction yielded mainly the eliminated product viz. **41** in 71% yield and the reduced product **46** in 17% yield. This compound **46** had comparable ^1H NMR data with that of **44**. Thus peaks at δ 0.95 - 1.2 (3H, d, $-CHCH_3$, J = 7 Hz), 3.2-3.6 (1H, m, $-CH(OCH_3)$), 3.3 (3H, s, $-OCH_3$), 3.4 (2H, d, $-OCH_2$, J = 5 Hz), 4.1 (1H, s, -CHPh), 6.95-7.7 (7H, m, aromatic and $=CH_2$ protons) were observed. In its mass spectrum M^+ peak at m/z 231 was found. In this case also ligand exchange[19] from HgOAc to HgCl with NaCl followed by reduction with $NaBH_4$ was attempted. However there was no difference in the product distribution.

For exploring another approach we considered the possibility of forming the bromohydrin **47** which could subsequently be reacted with $n\text{-}bu_3SnH$/AIBN to effect radical cyclisation[20]. The formation of bromohydrin (86% yield) was easily carried out by reacting **41** with N-bromosuccinimide (NBS) in DMSO-H_2O[21]. The ^1H NMR spectrum of **47** showed peaks at δ 3.2 (1H, s, -OH), 3.47 (2H, d, $-CH_2Br$, J = 8 Hz), 3.57 (2H, d, $-OCH_2$, J = 8 Hz), 3.58-4.1 (1H,

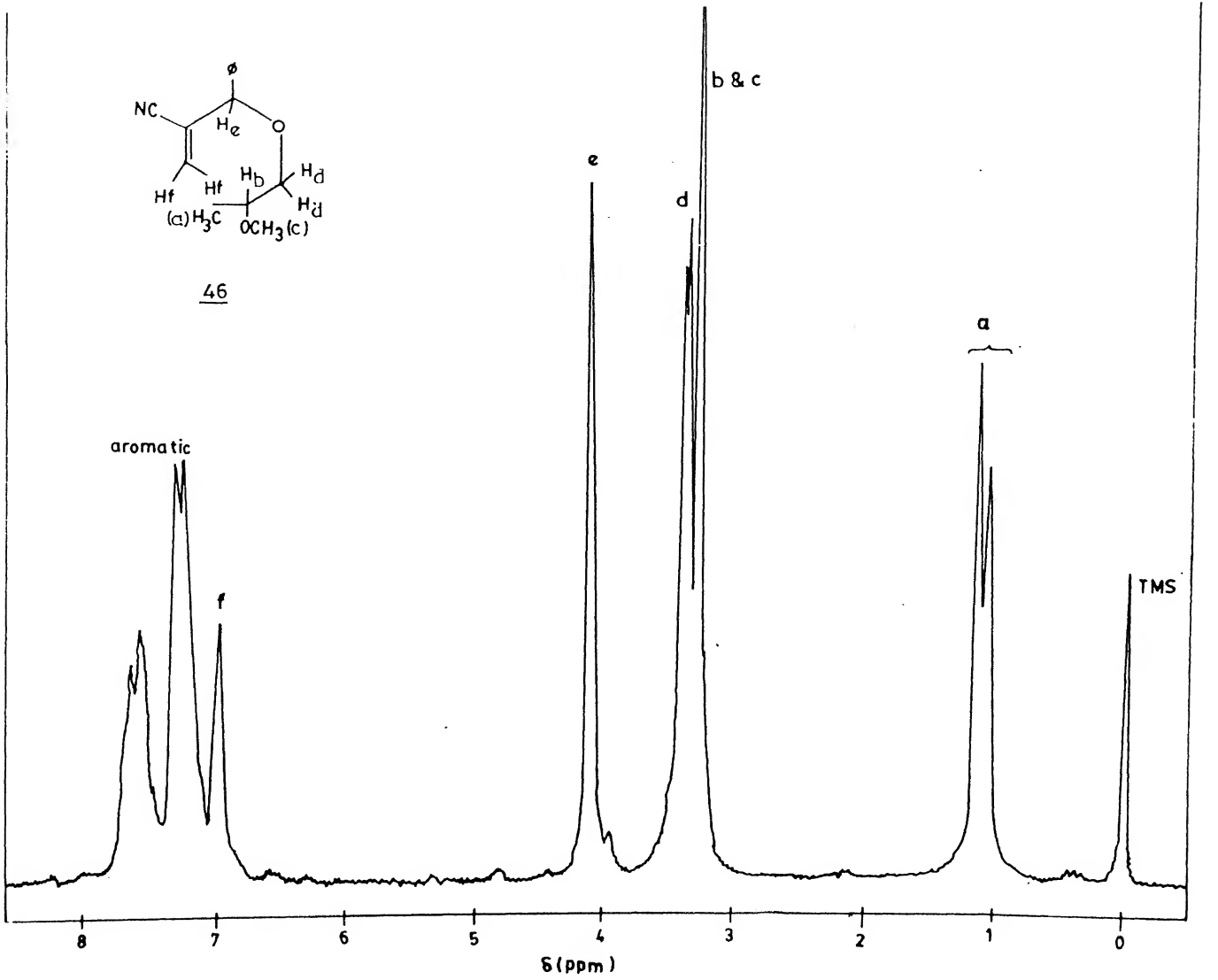


Figure III.3: ^{1}H NMR spectrum (60 MHz) of **46**

m, -CHOH), 4.2 (1H, s, -CHPh), 6.93-7.8 (7H, m, vinylic and aromatic protons). Its IR spectrum showed peaks at 2210 ($\nu_{C\equiv N}$), 3440 (ν_{-O-H}) cm^{-1}. Treatment of **47** with nbu_3SnH[22]/AIBN in refluxing benzene gave a mixture of compounds whose acetylation with acetic anhydride, triethylamine, DMAP followed by purification by column chromatography gave **43** and **44** in 22% and 32% yield respectively. Spectral data of these compounds were identical to the ones obtained via acetoxymercuration procedure. For comparison purpose and also to find the difference in the yields of the products **43** and **44** acetylation of **47** followed by radical cyclisation was attempted. Acetylation of bromohydrin was easily carried out using standard acetylation procedure and the bromo acetate **49** was characterised spectroscopically (cf.: III.3.10). Radical cyclisation was found to have marginal effect on the product distribution. Thus, compounds **43** and **44** were obtained in 28% and 30% yield respectively. Since the reduction of the halide was competing with the cyclisation we considered the possibility of using iodohydrins and iodoacetates to compare the differences if any. The iodohydrin **48** was prepared from **41** by reacting it with N-iodosuccinimide (NIS), DMSO - H_2O water under similar condition as the one followed for bromohydrin **47** preparation. The corresponding acetate was also prepared using standard acetylation procedure and both these compounds were characterised spectroscopically. The reaction of the iodohydrin **48** with $n\text{-}bu_3SnH$/AIBN followed by acetylation of the crude product gave 22% of the cyclised product **43** and 29% of the reduced one **44**. On the other hand, the iodoacetate **50** under similar conditions gave 24% of the cyclised product and 48% of

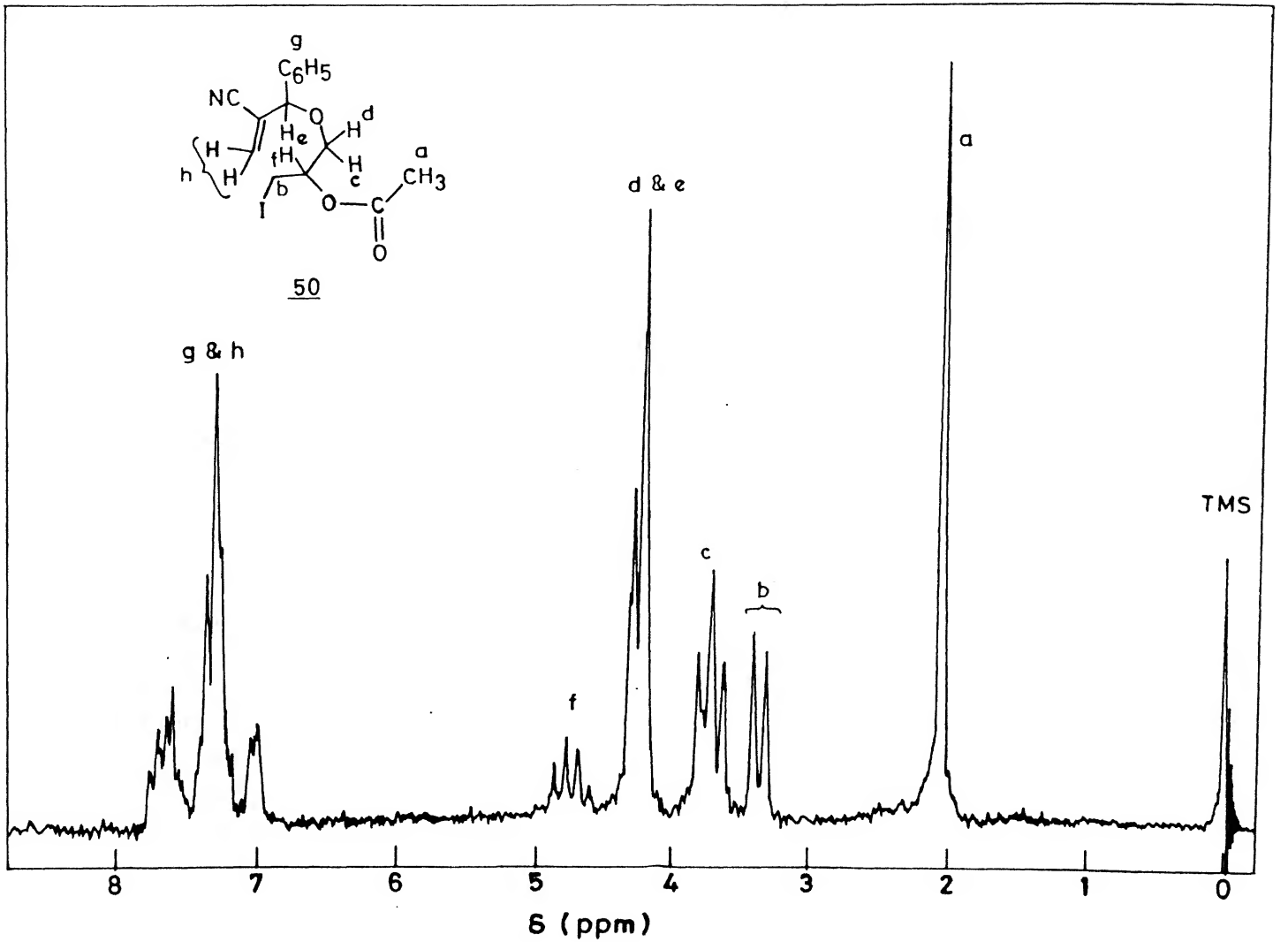


Figure III.4: ^{1}H NMR spectrum (60 MHz) of **50**

The above model study towards the synthesis of zoapatanol suggests that the route adopted is a quick entry into such oxepane systems. Appropriate functionalities at 2', 3' and 6' positions which would allow the initial Baylis Hillmann reaction, halohydrin formation followed by intramolecular radical cyclisation will give the desired zoapatanol **1**. One such possibility is shown in Fig. 15. This requires Baylis-Hillmann reaction on nitroethylene **51** with methyl pyruvate followed by the above described strategy. This nitro group is expected to yield the carbonyl group after the Nef reaction and thus it could be converted into alcohol.

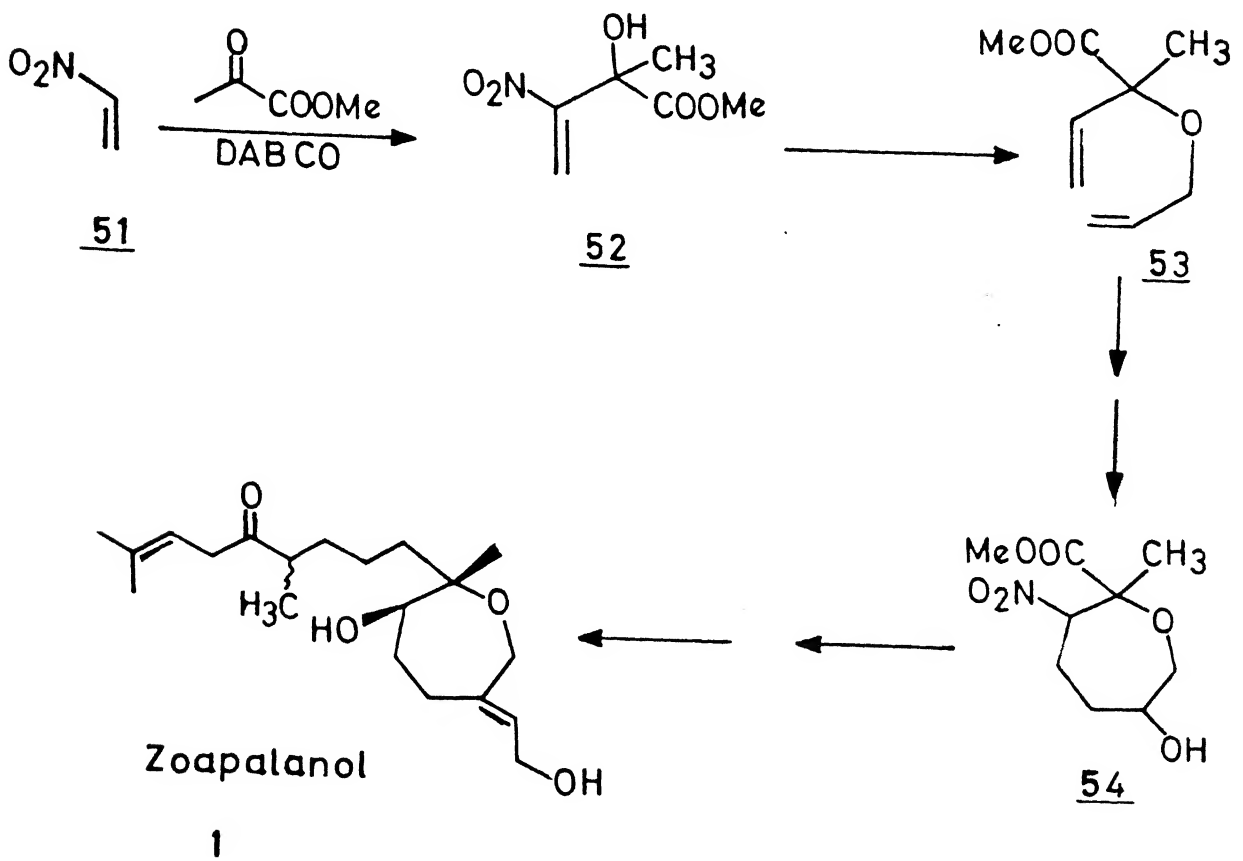


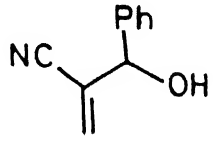
Figure 15

III.3 Experimental Section

The detils of the instruments used are the same as described in the section I.3. Acrylonitrile, triethylamine were distilled freshly before use. DABCO was purified by sublimation.

III.3.1 Preparation of 2-(1-hydroxy benzyl)-acrylonitrile: (40)

A mixture of benzaldehyde (1.02 ml, 10 mmol), acrylonitrile (0.99 ml, 15 mmol) and DABCO (0.16 8 g,1.5 mmol) was stirred at room temperature for 40 hours. After that the reaction mixture was taken up in ether (15 ml x 2) and washed with 2N hydrochloric acid (5 ml), aqueous sodium bicarbonate solution (5 ml), water (5 ml) and finally dried over anhydrous sodium sulphate. Solvent was removed and the residue was distilled to afford 1.13 g of 2-(1-hydroxy benzyl)- acrylonitrile **40**.



Yield 71%

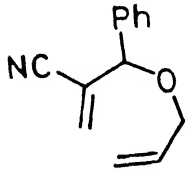
b.p. 140°C/2 mm (Lit[13] 125/2mm)

IR spectrum (neat) ν_{max}: 3460 , 2240 (-OH,-C ≡ N) cm^{-1}

^1H NMR spectrum (CCl_4): δ 7.2 (5H, br. s, aromatic proton), 5.8 (2H, d, $=CH_2$), 5.0 (1H, s, >CHOH), 3.4 (1H, br. s, >CHOH)

III. 3.2: Preparation of diallyl ether: (41)

To a stirred suspension of sodium hydride (50% dispersion in mineral oil, 150 mg, 3 mmol) in (2 ml) dry tetrahydrofuran (THF) was added 2-(1-hydroxy benzyl) acrylonitrile (318 mg, 2 mmol) at $0^{\circ}C$ and stirring was continued for half an hour. To this allyl bromide (363 mg, 3 mmol) in THF(0.5 ml) was added slowly at $0^{\circ}C$ and it was allowed to stir for 6 more hours. After the completion of the reaction (checked by TLC) the reaction mixture was taken up in ether (15 ml) and washed with 2N hydrochloric acid (5 ml), aqueous sodium bicarbonate solution (5 ml), water (5 ml) and subsequently brine. It was dried over anydrous sodium sulphate and after filtration the solvent was removed and the residue purified using column chromatography to afford 241 mg of the diallyl ether **41** (Eluent : ethyl acetate: petroleum ether 60-$80^{\circ}C$ = 7:93).



Yield 61%

A thick colourless oil

IR spectrum (neat) ν_{max}: 2210(s) (-C≡N) cm^{-1}

^1H NMR spectrum (CCl_4): δ 7.85-6.97 (7H, m, aromatic protons and CH_2=C-CN), 6.2-5.5 (1H, m, HC=CH_2), 5.45-5.0 (2H, m, H_2C = CH-) 4.2-3.9 (3H, m, >HC-O-CH_2-)

Mass spectrum (m/z) 199 (M^+); 158 ($M^+ - C_3H_5$); 142 ($M^+ - C_3H_5O$);

Anal. Calcd. for: $C_{13}H_{13}ON$: C, 78.39; H, 6.53;

Found : C, 78.21; H, 6.6%

III.3.3 Acetoxy mercuration of 41

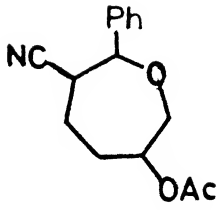
In a round bottom flask mercuric acetate (214 mg, 0.67 mmol) was taken in acetic acid (1.5 ml) at 10°C and compound **41** was added to this mixture slowly with stirring. After 45 min, the left over acetic acid was removed under reduced pressure to obtain **42A** in 90% yield which was used further without purification.

III.3.4 Demercuration of 42A

Compound **42A** obtained in step III.3.4 was taken in 3 ml of dichloromethane. Sodium borohydride (0. 056 g, 1.5 mmol) in 2 N NaOH solution (1 ml) was slowly added into the rection mixture with cooling by an ice bath. After the completion of addition the reaction was allowed to stir for eight hours. The reaction mixture was filtered through celite to remove mercury. The filtrate was worked up with ether and washed with water, brine and dried over anhydrous sodium sulphate. After removal of ether in the rotary evaporator the crude product so obtained was purified by column chromatography (eluents: petroleum ether 60-80/ ethyl acetate =95:5). Compound **43**, **44**, **41** were obtained in 9%, 15% and 68% yield respectively.

Compound (43)

A yellow coloured liquid



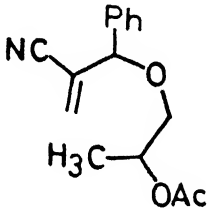
IR spectrum (neat) ν_{max}: 2218, 1740 ($-C\equiv N, -O-CO-CH_3$) cm^{-1}

^1H NMR spectrum (CCl_4): δ 7.16 (5H, br. s, aromatic protons), 4.33-3.26 (4H, m, -CHOAc, -OCHPh, $-O-CH_2-$ with a doublet centering at δ 4.2, J = 7 Hz), 3.23-2.66 (1H, m, -CHCN), 2.1-1.93 (3H, s, $-OCO-CH_3$), 1.8-0.8 (4H, m, 2 methylenes)

Mass spectrum (m/z): 259 (M^+)

Compound (44)

A colourless liquid



IR spectrum (neat) ν_{max} : 2208, 1730 ($-C\equiv N, -OCO-CH_3$) cm^{-1}

^1H NMR spectrum (CCl_4): δ 7.77-6.19 (7H, m, aromatic protons and $=CH_2$), 4.93 (1H, sextet, -CHOAc), 4.13 (1H, s, -O-CH-Ph), 3.47 (2H, d, $-OCH_2$, J = 5 Hz), 1.94, 1.9 (3H, 2s, $-O-COCH_3$), 1.23 (3H, d, $-CH-CH_3$, J = 6 Hz)

Mass spectrum (m/z): 259 (M^+)

III.3.5 Methoxy mercuration of (41)

Mercuric acetate (1 mmol) was dissolved in (1:1) mixture (2 ml) of methanol and dry THF. The reaction flask was cooled by

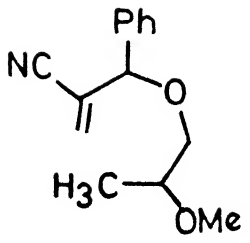
ice water bath and compound **41** (1 mmol) added to it dropwise with stirring. After the addition was completed it was allowed to stir for 45 minutes. The left over methanol and THF were removed under reduced pressure. Compound **42B** so obtained was used in the next step without purification.

III.3.6 Demercuration of 42B

Compound **42B** obtained in step III.3.5 was dissolved in a mixture of dichloromethane and methanol (0.5 ml). Sodium borohydride (1.5 mmol) was dissolved in 2 N NaOH solution (1ml) which was added dropwise to the reaction mixture at 0°C. After the addition was completed the reaction mixture was allowed to stir for 12 hrs. The reaction mixture was filtered to remove mercury and the filtrate was worked up with ether (2 x 15 ml) followed by water (5 ml) and brine (5 ml) respectively. The organic layer was dried over anhydrous sodium sulfate and the ether removed in the rotary evaporator. The crude product so obtained was purified by column chromatography. (eluent. pet ether (60-80°C)/ethyl acetate=94:6). Compound **41** and **46** were obtained in 71% and 17% yield respectively. The cyclised product could not be isolated as it was always contaminated with the reduced product **46** due to very close Rf values. But the spectral analysis of the crude reaction mixture clearly showed that the cyclised product **45** had formed in less than 7% yield.

Compound (46)

A colourless oil



IR spectrum (neat) ν_{max}: 2210 (-C ≡ N) cm^{-1}

^1H NMR spectrum (CCl_4): δ 7.7-6.95 (7H, m, aromatic and $=CH_2$ protons), 4.1 (1H, s, -CHPh), 3.4 (2H, d, $-OCH_2$, J = 5Hz), 3.3 (3H, s, $-OCH_3$), 3.6-3.2 (1H, m, $-HC-OCH_3$), 1.2-0.95 (3H, d, $-CHCH_3$, J = 7 Hz)

Mass spectrum (m/z): 231 (M^+)

Anal. Calcd. for $C_{14}H_{17}O_2N$: C, 72.72; H, 7.35%

Found: C, 73.2; H, 8.05%

III.3.7 Ligand Exchange[19] and Demercuration of 42B

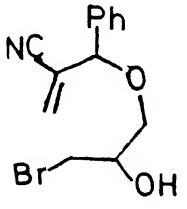
Compound **42B** was added to a mixture of water (1 ml) and saturated NaCl solution (0.5 ml) with stirring. After 20 minutes of stirring a sticky pale yellow precipitate was separated out which was allowed to settle down. The supernatant water was slowly decanted and 1N NaOH (1 ml) and cosolvent DMF (2.5 ml) were added to the precipitate. This mixture was cooled in an ice bath and $NaBH_4$ (0.056 g, 1.5 mmol), dissolved in 1N NaOH was added dropwise to it. After 6hrs., a colourless solution was observed with the separation of mercury metal. Fitration of mercury followed by workup (cf: III.3.6) gave compound **41** and **46** in 59% and 22% yield respectively.

III.3.8 Preparation of bromohydrin[21]: (47)

Diallyl ether **41** (200 mg, 1 mmol) was taken in 1.5 ml DMSO and 0.075 ml(4 mmol) of water and the reaction mixture was cooled with ice water mixture to 10°C. Freshly recrystallised, N-bromosuccinimide (223 mg, 1.25 mmol) was added to it in portion and the reaction mixture thoroughly stirred at 10°C. After 1 hr the reaction mixture was worked up by adding 1 ml satd $NaHCO_3$ solution followed by extraction with ether (3 x 10 ml) and washing with water (5 ml) and brine (5 ml) respectively. The organic layer was dried over anhydrous Na_2SO_4 and the evaporation of the solvent gave the crude product which was purified by column chromatography (eluent: (60-80°C) pet ether: ethyl acetate, 92:8) to obtain 250 mg (85%) of pure **47**.

Compound (47)

A yellow coloured oil



IR spectrum (neat) ν_{max}: 3440 (Br), 2210 (s) (-OH, -C ≡ N) cm^{-1}

^1H NMR spectrum (CCl_4): δ 7.8-6.93 (7H, m, aromatic protons and = CH_2), 4.2 (1H, s, -CHPh), 4.1-3.58 (1H, m, -CHOH), 3.57 (2H, d, $-OCH_2$, J = 8 Hz), 3.47 (2H, d, $-CH_2$ Br, J=8 Hz), 3.2 (1H, s, -OH)

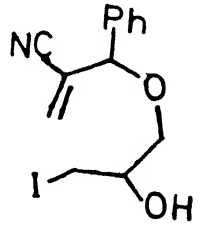
Mass spectrum (m/z): 296 (M^+)

III.3.9 Synthesis of iodohydrin: (48)

Iodohydrin **48** was synthesised following the same method as described for the synthesis of compound **47** (Sec. III.3.8) except that instead of NBS, N-iodosuccinimide (NIS) (281 mg, 1.25 mmol) was used. The crude iodohydrin was purified by column chromatography (eluent: Pet ether (60-80°C)/ethyl acetate: 93/7) to obtain pure **48**.

Compound (48)

Yield- 80%



A yellow coloured oil

IR spectrum (neat) ν_{max}: 3460, 2210 (-OH, -C ≡ N) cm^{-1}

^1H NMR spectrum (CCl_4): δ 7.82-7.21 (7H, m, vinylic and aromatic protons), 4.53 (1H, s, -CHPh), 4.3-4 (1H, m, -CHOH), 3.83 (2H, d, $-OCH_2$, J = 6 Hz), 3.51 (2H, d, $-CH_2I$, J = 4 Hz) 3 (1H, s, -CHOH)

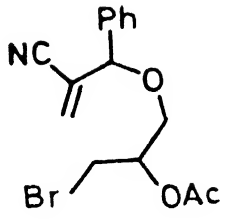
Mass spectrum (m/z): 343 (M^+)

III.3.10 Acetylation of bromohydrin

The bromohydrin **47** (2 mmol) was acetylated by following the usual procedure as described in the Sec. I.12. Purification by column chromatography (eluent: pet ether (60-80°C/ ethyl acetate: 95/5) gave pure **49**.

Compound (49)

Yield 96%



A yellow coloured liquid

IR spectrum (neat) ν_{max}: 2205, 1730 (-C ≡ N, -O-CO-CH_3) cm^{-1}

^1H NMR spectrum (CCl_4): δ 7.9-7.1 (7H, m, = CH_2 and aromatic protons), 5.2-4.8 (1H, m, >CHOAc), 4.4-4.06 (2H, m, s of HC-Ph and d of -O-CH_a-H_b), 3.7 (1H, d, -O-CH_aH_b, J = 5 Hz), 3.6-3.4 (2H, m, -CH_2-Br), 2.0 (3H, s, -O-CO-CH_3)

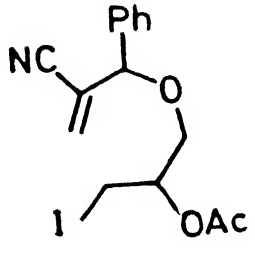
Mass spectrum (m/z): 338 (M^+)

III.3.11 Acetylation of iodohydrin

Iodohydrin **48** (2 mmol) was acetylated following the same procedure as given in Sec. I.12. Purification by column chromatography (eluent: pet ether (60-80°C)/ ethyl acetate: 95/5) gave **50**.

Compound (50)

Yield 80%



A yellow coloured liquid

IR spectrum (neat) ν_{max} : 2210, 1730 (-C ≡ N, -$COCH_3$) cm^{-1}

^{1}H NMR spectrum (CCl_4): δ 7.66-6.97 (7H, m, aromatic and = CH_2), 4.75-4.45 (1H, m, >CHOAc), 4.27-4 (2H, m, -CHPh and d of -O-CH_dH_c) , 3.65(1H, m,-O-CH_dH_c), 3.3 (2H, d, $-CH_2I$, J=7Hz), 2.06 (3H, s, -O-CO-CH_3)

Mass spectrum (m/z): 385 (M^+)

III.3.12 TBTH induced radical cyclisations of bromohydrin.

A mixture of bromohydrin **47** (115 mg, 0.388 mmol) was taken in 7 ml of benzene and freshly distilled TBTH (225 mg, 0.776 mmol) and AIBN(0.02g, 0.12 mmol) were added to it under argon atmosphere. The reaction mixture was refluxed for 12 hrs and at the end of this period benzene was removed under reduced pressure. The crude product was washed with cold petroleum ether to remove the unwanted organotin compound and the residue was acetylated by treating it with a mixture of triethylamine (0.15 ml, 1.08 mmol), acetic anhydride (0.07 ml, 0.74 mmol) and catalytic amount of DMAP in dichloromethane (5 ml). The reaction mixture was allowed to stir at 30°C for 20 hrs and then was worked up by following the same procedure as described in sec. I.12. The crude acetate was purified by column chromatography (eluent: pet-ether (60-80°C)/ ethyl acetate, 92:8) to obtain compound **43** and **44** were in 22% and 32% yield respectively.

III. 3.13 TBTH induced radical cyclisations of iodohydrin 48

Procedure:

Following the previous procedure iodohydrin **48** (0.343g,1 mmol) was refluxed with TBTH (0.580g, 2 mmol), and AIBN (0.05g,

0.30 mmol) under argon atmosphere in 7 ml benzene. The reaction mixture was worked up by following the same method as adopted in the case of bromohydrin. The crude reaction mixture was acetylated and products obtained thereby purified by column chromatography (eluent: pet ether (60-80°C)/ ethyl acetate, 94:6) to obtain compounds **43** and **44** in 22% and 29% yield respectively.

III. 3.14 TBTH induced radical cyclisation of bromoacetate 49

Procedure:

Bromoacetate **49** (0.338g, 1mmol) was taken with freshly distilled TBTH (0.58g, 2 mmol) and AIBN (0.034g,0.21 mmol) in 8 ml of benzene under argon atmosphere. The reaction mixture was refluxed for 10 hr. Benzene was removed under reduced pressure and the crude product was washed with cold pet ether (60-80°C) to remove unwanted organotin compound. The residue was then purified by column chromatography (eluent: ethyl acetate and petroleum ether 60-80°C, 7:93) to obtain **43** and **44**. in 28% and 30% yield respectively.

III. 3.15 TBTH induced radical cyclisation of iodoacetate 50

Procedure:

Following the above procedure (0.385g,1 mmol) iodoacetate was used for TBTH induced radical cyclisation. After column chromatography purification products **43** and **44** were obtained in 24% and 48% yield respectively.

References

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